

EXHIBIT 2

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and Fluidigm Canada Inc.*

**UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION**

FLUIDIGM CORPORATION, a Delaware
corporation; and FLUIDIGM CANADA
INC., a foreign corporation,

Plaintiffs,

v.

IONPATH, INC.,
A Delaware corporation,

Defendant.

Case No. 3:19-cv-05639

~~FIRST~~SECOND AMENDED
COMPLAINT FOR PATENT
INFRINGEMENT AND INTENTIONAL
INTERFERENCE WITH
CONTRACTUAL RELATIONS

JURY TRIAL DEMANDED

**Judge: Honorable William Alsup
Complaint filed: September 6, 2019**

Plaintiffs, Fluidigm Corporation and Fluidigm Canada Inc. (collectively, “Fluidigm”), make the following allegations in support of their ~~First~~Second Amended Complaint against Defendant, IONpath, Inc. (“IONpath”):

THE NATURE OF THE ACTION

1. This is an action for intentional interference with contractual relations and patent infringement arising out of IONpath’s deliberate, willful, and ongoing infringement of Fluidigm’s well-established rights.

2. Fluidigm provides innovative tools for biotechnology research including, for example, mass cytometry systems and methodologies that are used by customers ~~such-~~as including, for example, leading academic, governmental, and private institutions worldwide.

3. Fluidigm is and has become an industry leader, in part, through its careful and extensive research, development, investment, and protection of its intellectual property rights including, among others, certain patent families dating back to at least 2004, as well as through the employ of, and consulting with, leading scientists in fields related to mass cytometry.

4. Consultants who were under contract with Fluidigm, and while retained by Fluidigm, formed a directly competing entity – IONpath – in partnership with other individuals. Even more distressing, the new IONpath enterprise has been developing a directly competing product to Fluidigm’s mass cytometry systems requiring the use and implementation of Fluidigm’s patented methodologies.

5. ~~Indeed,~~ Fluidigm learned that IONpath was using Fluidigm’s proprietary antibodies and reagents to test a mass cytometry system that IONpath was purportedly

developing, the MIBIScope. Concerned that IONpath was infringing upon Fluidigm's rights, ~~and that IONpath was encouraging~~ as well as inducing Fluidigm's customers to breach their contracts with Fluidigm regarding the antibodies and reagents, Fluidigm repeatedly contacted IONpath in an effort to persuade IONpath to voluntarily cease its improper and unlawful conduct.

6. Instead of heeding Fluidigm's warnings, and ceasing its conduct, in September 2018, IONpath published an article and issued press releases touting the results IONpath obtained using Fluidigm's patented methodologies. ~~Recently~~ Thereafter, IONpath began aggressively marketing the date that it was going to formally, commercially, launch ~~date of its new and infringing product set for late 2019.~~ its new and infringing products to additional customers including the MIBIScope and MIBItag reagents. Troubled by IONpath's disregard for Fluidigm's warnings, on September 24, 2018, Fluidigm again demanded IONpath refrain from interfering with Fluidigm's contracts with its customers and additionally put IONpath on notice of one of Fluidigm's patents that Fluidigm was concerned IONpath was infringing. IONpath ignored Fluidigm's September 2018 identification of its patents and IONpath's tortious and wrongful conduct, and continued to sell its infringing products and cause Fluidigm's customers to breach their contracts with Fluidigm.

7. Even after Fluidigm filed this lawsuit, and after IONpath was on further notice of its infringement and that its continued and proposed acts constitute infringement, IONpath announced the commercial launch of its infringing product, the MIBIScope, on November 5, 2019, and participated in a conference further promoting and instructing third-parties on how to use and infringe upon Fluidigm's patents using IONpath's infringing products and continued to

publish papers detailing MIBIScope’s implementation of the infringing conduct. Not only that, but on February 11, 2020, IONpath announced an infringing service it would offer customers where IONpath’s “expert team of engineers, pathologists and data scientists” will use the infringing MIBIScope platform to image forty plus biomarkers for its customers.

8. ~~7.~~ IONpath’s publications and press releases establish that not only had IONpath been developing its mass cytometry system employing Fluidigm’s antibodies and reagents, but also ~~wholesale~~-adopted and is using Fluidigm’s patented methods and systems – and is making, using, offering to sell, and is selling its infringing products ~~and~~ systems, and services in the marketplace.

9. ~~8.~~ IONpath’s conduct, including its refusal to cease its infringing conduct even after Fluidigm filed this lawsuit, leaves Fluidigm with no option but to proceed with this ~~lawsuit~~litigation in order to prevent IONpath from continuing its improper, wrongful, widespread, and willful infringement of Fluidigm’s patented technologies. In addition to seeking the cessation of IONpath’s wrongful conduct, it also seeks redress for IONpath’s past direct infringement, post-suit direct and indirect infringement, and tortious interference with Fluidigm’s contractual relationships with its customers.

PARTIES

10. ~~9.~~ Fluidigm Corporation is a Delaware corporation with a principal place of business located at 7000 Shoreline Court, Suite 100, South San Francisco, California 94080.

11. ~~10.~~ Fluidigm Canada Inc. is an Ontario corporation organized under the laws of Ontario with its principal place of business at 1380 Rodick Rd., Markham, Suite 100, Ontario,

L3R 4G5 Canada. Fluidigm Canada Inc. is a wholly owned subsidiary of Fluidigm Sciences Inc., a Delaware corporation, which is a wholly owned subsidiary of Fluidigm Corporation.

12. ~~11.~~ On information and belief, IONpath is a Delaware corporation with a principal place of business within this judicial district at 960 O'Brien Dr., Menlo Park, California 94025.

JURISDICTION AND VENUE

13. ~~12.~~ This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a) because this is an action for, in part, patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, *et seq.*, including §§ 271 and 281. This Court has subject matter jurisdiction over the tortious interference claim pursuant to 28 U.S.C. § 1367(a).

14. ~~13.~~ On information and belief, IONpath is subject to this Court's specific and general personal jurisdiction, pursuant to due process and/or the California Long Arm Statute.

15. ~~14.~~ Venue is proper in this District under 28 U.S.C. §§ 1391(b) and 1391(c) because IONpath resides and does substantial business in this District, and has committed acts of patent infringement and tortious interference in this District. Venue is also proper in this District under 28 U.S.C. § 1400(b) because IONpath is subject to personal jurisdiction in this District, has a principal place of business in this District, has committed and continues to commit acts of infringement in this District, and a substantial part of the events giving rise to the claims occurred in this District.

BACKGROUND

I. FLUIDIGM'S INDUSTRY LEADING ROLE IN MASS CYTOMETRY

16. ~~15.~~ Fluidigm is a leading provider of cutting-edge tools, systems, and methods for biotechnology research including, among other things, microfluidics systems, suspension-based mass cytometry and Imaging Mass Cytometry™. Fluidigm's customers include, for example, leading academic, government, pharmaceutical, biotechnology, and plant and animal research laboratories worldwide.

17. ~~16.~~ Fluidigm's proprietary technologies enable the scientific discovery and investigation in critical areas of research, provide meaningful insights into health and disease, and accelerate the development of effective therapies including, for example, in the areas of cancer, immunology and immunotherapy.

18. ~~17.~~ Mass cytometry is a technique for investigating structures and biomarkers on the cellular level, including intracellular features. Fluidigm's proprietary CyTOF®, Helios™ and Hyperion™ mass cytometry technologies allow for the interrogation of more than 40 markers simultaneously on thousands of individual cells, which can enable the identification of new cell types, functions, and biomarkers indicative of different disease states and/or responsiveness to therapeutic treatments. Fluidigm's Hyperion™ system combines Fluidigm's CyTOF technology with imaging capabilities to interrogate tissues at subcellular resolution while preserving the sample's tissue architecture for cutting-edge image analysis.

19. ~~18.~~ Fluidigm's proprietary Maxpar® reagents provide critical state-of-the-art labelling tools for identification of targets using Fluidigm's proprietary mass cytometry techniques, methods, and systems.

20. ~~19.~~ Foundational aspects of mass cytometry technology were developed, in part, by Dr. Scott Tanner as an improvement over prior fluorescence-based techniques. Specifically, while fluorescence-based flow cytometry techniques only identified a limited number of markers because of spectral overlap of fluorophores, mass cytometry uses specialized reagents – metal tags attached to specific antibodies – that can be quantified using high resolution mass spectrometry. The ability to use stable metal isotopes not normally found in biological systems, with target-specific antibodies, in a transient single cell, allows for the quantification of multiple parameters in a cell, both on a cell-by-cell basis, as well as across potentially thousands of cells. The invention of this technique involved leveraging of innovations in areas including, for example, mass spectrometry and biotechnology, specifically: providing ionized and atomized elemental tags from individual cells, time-of-flight technology and ion optics for detecting a plurality of element tags from individual cells, and polymer and metal ligand chemistry.

21. ~~20.~~ Dr. Tanner and others, including Drs. Vladimir I. Baranov and Dmitry R. Bandura, further developed the proprietary technique and, based upon their inventions, certain patent applications were filed. Shortly thereafter, the inventors started their company DVS Sciences, Inc. ("DVS"), and licensed certain aspects of their patent applications. Fluidigm acquired DVS in 2014, purchased the proprietary technology – including the patent rights relating to the technique, systems, and methods, and continued to work on and develop the

technology, systems and methods for mass cytometry, including the CyTOF[®] mass cytometer, the next generation Helios[™] mass cytometer released in 2015, and the Hyperion[™] Imaging System released in 2017.

22. ~~21.~~ While at DVS, Dr. Vladimir I. Baranov also collaborated with the University of Toronto to further develop CyTOF[®] technologies, including specialized reagents for mass cytometry techniques. As part of this work, patent applications for certain reagents and technologies were filed which were assigned to DVS and subsequently assigned to Fluidigm. Fluidigm has continued to work on and develop the technology, systems and methods for mass cytometry, including the Maxpar[®] antibodies and reagents for use with these systems.

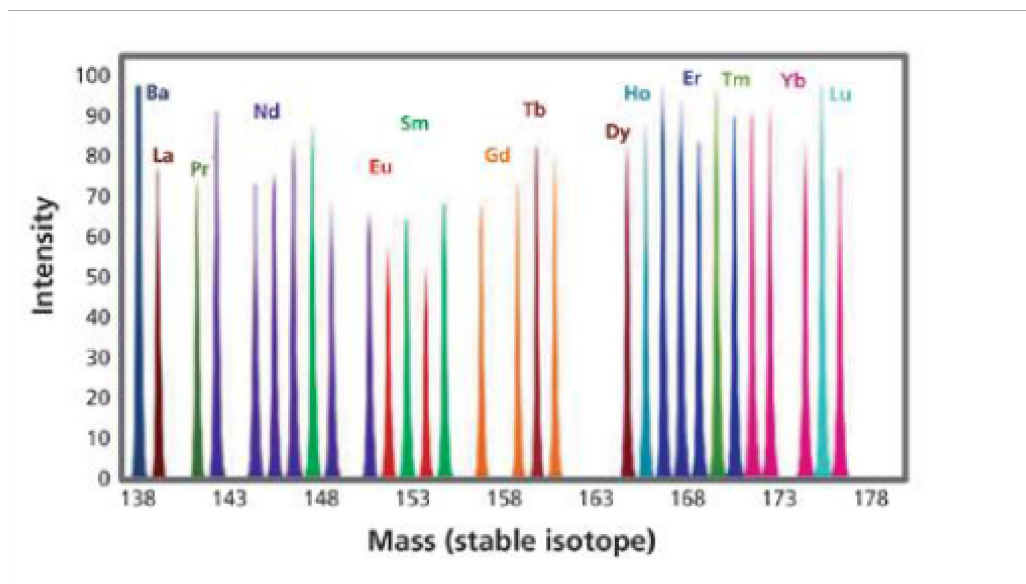
23. ~~22.~~ In performing a mass cytometry analysis using Fluidigm's patented methodologies, the sample of interest (e.g., a suspension of cells or tissue sample) is labelled by introducing reagents comprising metal tags attached to antibodies that are specific to targets of interest within the sample, a process often referred to as "staining" of the sample. The antibodies specifically bind to the targets of interest if present in the sample, which may be specific cellular components, such that the targets are labelled with the particular metal tag connected to the bound antibody. The metal tags may be different elemental metal isotopes (such as lanthanide isotopes) that differ from each other in their varying weights.

24. ~~23.~~ The reagents used for labelling provide a plurality of antibodies with metal tags, with each labelling antibody that is specific for a particular target being attached to a metal tag having a different weight than the metal tags of other labelling antibodies that are specific for other targets. A washing step may be performed to remove any unreacted reagent that did not

bind to a target, such that generally only those labels that find and bind to their targets remain in the sample.

25. ~~24.~~ To quantitatively analyze the labelled sample, a procedure is performed to release the metal tags from the sample, and the ionized metal tags are provided to a device known as a mass spectrometer, which is capable of detecting and measuring the mass to charge ratio of the resulting ions. Because the metal tags have different weights (i.e., a different weight for each target-specific antibody), the mass spectrometer is capable of detecting and distinguishing the different metal tags used for labelling, meaning that information related to the presence or absence of the antibody-bound targets in the sample is obtained. The output from this detection can be analyzed and processed to provide multiplex information at the subcellular level, including comprehensive functional and phenotypic characterization of complex systems at the single-cell level of samples containing potentially thousands of cells.

26. ~~25.~~ Using Fluidigm's proprietary technique and technology, an example output of isotope signals generated from single cells is illustrated below for various metal isotopes:



27. ~~26.~~ In addition, Fluidigm is the leading industry provider of labelling antibodies and other reagents for use in mass cytometry. Specifically, Fluidigm offers the Maxpar[®] antibodies and reagents, which have been developed specifically for use with Fluidigm's proprietary mass cytometry technology. The Maxpar[®] antibodies and reagents provide for the labelling of samples with antibodies conjugated to metal tags to allow for multiplex imaging (i.e. the evaluation of multiple targets in the sample), and thus are an important component in state of the art mass cytometry analysis.

28. ~~27.~~ Fluidigm's mass cytometry products have been critical for breakthrough discoveries in numerous research areas including, for example, in biomarker screening, immunotherapy, immunology, immunophenotyping, infectious disease/microbiology, inherited disease detection, neurology, and oncology.

II. **FLUIDIGM’S ASSERTED PATENTS**

29. ~~28.~~ Fluidigm has carefully protected its inventions and cutting-edge technologies with a range of intellectual property rights. In particular, the U.S. Patent and Trademark Office (“the Patent Office”) has awarded Fluidigm numerous patents covering its extremely valuable technologies.

A. ***‘386 Patent***

30. ~~29.~~ Fluidigm is the assignee of all right, title, and interest in and to U.S. Patent No. 10,180,386 (the “‘386 Patent”), titled “Mass Spectrometry Based Multi-Parametric Particle Analyzer.” The Patent Office duly and properly issued the ‘386 Patent on January 15, 2019. A true and correct copy of the ‘386 Patent is attached hereto as Exhibit A.

31. ~~30.~~ Fluidigm is the owner of all right, title, and interest in the ‘386 Patent, including all rights to pursue and collect damages for past, present, and future infringement of the ‘386 Patent.

32. ~~31.~~ The Patent Office carefully examined the ‘386 Patent, and its associated patent family, over a period of years going back to 2004. In doing so, the Patent Office found that the inventions described and claimed in the ‘386 Patent are both new and not obvious in light of prior patents, publications, and other art, and determined that the claimed systems and methods are inventive and patentable.

33. ~~32.~~ The claims of the ‘386 Patent are generally directed to methods for analyzing cells by mass spectrometry. For example, claim 1 of the ‘386 Patent recites:

A method of sequentially analyzing single cells by mass spectrometry, comprising:

providing a sample containing a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the tagged antibodies is specific for a different analyte, and wherein each of the tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal;

vaporizing, atomizing, and ionizing multiple elemental tags from a single first cell of the plurality of tagged cells;

detecting, using mass spectroscopy, the elemental composition of the first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell;

vaporizing, atomizing, and ionizing multiple elemental tags from a single second cell of the plurality of tagged cells; and

detecting, using mass spectrometry, the elemental composition of the second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the second cell, wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially.

34. Further, exemplary claim 9 of the '386 Patent depends from claim 1, and recites:

The method of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope.

35. 33. The '386 Patent describes that the technology disclosed therein overcomes deficiencies in prior cell analysis methods, such as the issues with spectral overlap encountered in flow cytometry, to provide improved analysis of intracellular and cell surface characteristics. '386 Patent at column 2, lines 11-45, and Examples 1-13.

36. 34. Importantly, the technology and methods claimed in and covered by the '386 Patent are unique and novel and permit individuals to conduct extremely valuable analysis on a cellular level. The '386 Patent includes important insights including, among other things, the use of mass spectrometry on biological materials, an understanding of how to use the biological

materials (antibodies targeting analytes), time of flight analysis to allow for the separation of the lanthanide or noble metal tag by weight, and the understanding of how to use the different metal isotopes coupled with antibodies as reagents.

37. ~~35.~~ The ‘386 Patent, and its patent family, relate back to a provisional patent application filed on March 25, 2004, as well as, among others, U.S. Patent Nos. 9,952,134 (the “‘134 Patent”) and 7,479,630 (the “‘630 Patent”).

38. ~~36.~~ On information and belief, IONpath had prior notice of the ‘386 Patent and its patent family. Specifically, two of IONpath’s founders applied for a patent in 2011, publication number US2012/0077714 A1, citing to, among other sources, the ‘630 Patent, to which the ‘386 claims priority and which contains the same disclosure as the ‘386 patent. The two IONpath founders again referenced Fluidigm’s related ‘630 Patent in their 2013 list of references submitted to the Patent Office.

39. Further, IONpath indisputably also gained full notice and knowledge of the ‘386 Patent and IONpath’s infringement of one or more claims of the ‘386 Patent when it was served with the Original and First Amended Complaints in this lawsuit, served on September 23, 2019 and October 11, 2019, respectively.

B. ‘104 Patent.

40. ~~37.~~ Fluidigm Canada is the assignee of U.S. Patent No. 10,072,104 (the “‘104 Patent”), titled “Polymer Backbone Element Tags.” The Patent Office duly and properly issued the ‘104 Patent on September 11, 2018. A true and correct copy of the ‘104 Patent is attached hereto as Exhibit B.

41. ~~38.~~ Fluidigm Canada is the owner of all right, title, and interest in and to the '104 Patent, including all rights to pursue and collect damages for past, present, and future infringement of the '104 Patent.

42. ~~39.~~ The Patent Office found that the inventions described and claimed in the '104 Patent are both new and not obvious in light of prior patents, publications, and other art, and determined that the claimed systems and methods are inventive and patentable.

43. ~~40.~~ The claims of the '104 Patent are generally directed to methods for analysis of a sample. For example, claim 1 of the '104 Patent recites:

A method for the analysis of an analyte in a sample, comprising:

(i) incubating an element tagged affinity reagent with an analyte, the element tagged affinity reagent comprising an affinity reagent tagged with an element tag, the element tag comprising a linear or branched polymer having multiple metal-binding pendant groups, wherein each pendant group includes at least one metal atom or is capable of binding at least one metal atom, and wherein the affinity reagent specifically binds with the analyte, wherein the analyte is located within or on an intact cell;

(ii) separating unbound element tagged affinity reagent from bound element tagged affinity reagent; and

(iii) analyzing the element tag bound to the affinity reagent attached to the analyte of the intact cell by atomic spectroscopy, wherein analyzing occurs without prior acidification of the sample.

44. Further, exemplary claim 14 of the '104 Patent depends from claim 1, and recites:

The method of claim 1, wherein the affinity reagent is an antibody.

45. ~~41.~~ The '104 Patent describes that the mass spectrometry technology disclosed and claimed therein provides extremely valuable improvements over prior methods including, by

way of example, UV vis spectroscopy, HPLC, flow cytometry, ligand binding assays, and others, by allowing for multiplexing (determining the presence of multiple targets in a sample), improved sensitivity and improved selectivity. ~~402~~104 Patent at column 1, lines 35-60.

46. ~~42.~~ Fluidigm provided IONpath explicit notice of the '104 Patent on September 24, 2018, as discussed in more detail below.

47. Further, IONpath indisputably also gained full notice and knowledge of the '104 Patent and IONpath's infringement of one or more claims of the '104 Patent when it was served with the Original and First Amended Complaints in this lawsuit, served on September 23, 2019 and October 11, 2019, respectively.

C. ***'698 Patent***

48. ~~43.~~ Fluidigm is the assignee of all right, title, and interest in and to U.S. Patent No. 10,436,698 (the "'698 Patent"), titled "Mass Spectrometry Based Multi-Parametric Particle Analyzer." The Patent Office duly and properly issued the '698 Patent on October 8, 2019. A true and correct copy of the '698 Patent is attached hereto as Exhibit C.

49. ~~44.~~ Fluidigm is the owner of all right, title, and interest in the '698 Patent, including all rights to pursue and collect damages for past, present, and future infringement of the '698 Patent.

50. ~~45.~~ The Patent Office carefully examined the '698 Patent, and its associated patent family (including the '386 Patent discussed above), over a period of years going back to 2004. In doing so, the Patent Office found that the inventions described and claimed in the '698 Patent are

both new and not obvious in light of prior patents, publications, and other art, and determined that the claimed systems and methods are inventive and patentable.

51. ~~46.~~ The claims of the '698 Patent are generally directed to systems for analyzing cells in a sample by mass spectrometry. For example, claim 1 of the '698 Patent recites:

A system for sequentially analyzing single cells in a sample by mass spectrometry,

wherein the sample comprises a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the plurality of tagged antibodies is specific for a different analyte, and wherein each of the plurality of tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal;

wherein the system comprises:

a first device to vaporize, atomize, and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a single second cell of the plurality of tagged cells; and

a second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single first cell, and lanthanides and/or noble metals of the single second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single second cell, wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially.

52. Further, exemplary claim 6 of the '698 Patent depends from claim 1, and recites:

The system of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope.

53. ~~47.~~ The '698 Patent describes that the technology disclosed therein overcomes deficiencies in prior cell analysis systems, ~~such as the~~ including, by way of example, issues with

spectral overlap encountered in flow cytometry systems, to provide improved analysis of intracellular and cell surface characteristics. '698 Patent at column 2, lines 14-47, and Examples 1-13.

54. ~~48.~~ Importantly, the technology and systems claimed in and covered by the '698 Patent are unique and novel and permit individuals to conduct extremely valuable analysis on a cellular level. The '698 Patent includes, among other things, important insights into systems and devices for performing mass spectrometry on biological materials, such as biological samples stained with tagged antibodies targeting analytes, and systems and devices to detect lanthanides and/or noble metals that use time of flight analysis to allow for the separation of the lanthanide and/or noble metal tags by weight.

55. ~~49.~~ The '698 Patent, and its patent family, relate back to a provisional patent application filed on March 25, 2004, as well as, among others, the ~~2~~¹134 and ~~2~~¹630 Patents.

56. ~~50.~~ On information and belief, IONpath had prior notice of the '698 Patent and its patent family. Specifically, two of IONpath's founders applied for a patent in 2011, publication number US2012/0077714 A1, citing to, among other sources, the '630 Patent, to which the '698 claims priority and which contains the same disclosure as the '698 patent. The two IONpath founders again referenced Fluidigm's related '630 Patent in their 2013 list of references submitted to the Patent Office.

57. Further, IONpath indisputably also gained full notice and knowledge of the '698 Patent and IONpath's infringement of one or more claims of the '698 Patent when it was served with the First Amended Complaint in this lawsuit, served on October 11, 2019.

III. FLUIDIGM CONSULTANTS FORM IONPATH

A. Dr. Garry Nolan

58. ~~51.~~ In March 2014, Dr. Nolan along with Drs. Angelo and Bendall and several other authors, published a technical report (the “2014 Technical Report”) discussing their academic research on working with multiplexed ion beam imaging in the field of immunohistochemistry.

59. ~~52.~~ On May 16, 2014, Fluidigm entered into a Scientific Consulting Agreement (“Nolan Consulting Agreement”) with Professor Garry Nolan (“Dr. Nolan”). Pursuant to the Nolan Consulting Agreement, Fluidigm retained Dr. Nolan for the purpose of assisting Fluidigm with “the development and applications of mass cytometry-based instrumentation, including associated reagents,” defined in the Nolan Consulting Agreement as the “Field of Interest.”

60. ~~53.~~ In the Nolan Consulting Agreement, Dr. Nolan agreed:

[T]hat during the Term of this [Consulting] Agreement he will not directly or indirectly (i) provide any services in the Field of Interest to any other business or commercial entity, including without limitation research or other work for which any business or commercial entity has rights (e.g., patent rights, a right to a license, or a first or other right to negotiate a license), (ii) participate in the formation of any business or commercial entity in the Field of Interest, or (iii) solicit or hire away any employee or consultant of the Company.

Nolan Consulting Agreement at ¶ 5.

61. ~~54.~~ The Nolan Consulting Agreement contained appropriate carve-outs to allow and encourage Dr. Nolan to continue to work as an employee of the university of which he was employed as a professor. *Id.* The Nolan Consulting Agreement also limited its term to four years or upon earlier termination upon 30 day notice. *Id.* at ¶ 3.

62. ~~55.~~ The Nolan Consulting Agreement also required Dr. Nolan to disclose opportunities, as well as ~~direct project~~projects and inventions, to Fluidigm in the Field of Interest. *Id.* at ¶ 6. Importantly, the Nolan Consulting Agreement provided that Dr. Nolan “will use his best efforts (i) to disclose to the President of the Company, on a confidential basis, technology and product opportunities which come to the attention of [Dr. Nolan] in the Field of Interest, and any invention, improvement, discovery, process, formula, or method or other intellectual property relating to or useful in the Field of Interest (collectively “New Discoveries”), whether or not patentable or copyrightable, and whether or not discovered or developed by [Dr. Nolan], and (ii) with regard to any New Discoveries discovered or developed by [Dr. Nolan] at the Institution, to solicit or encourage the Institution to enter into an agreement with the Company to exclusively license such New Discovery to the Company.” *Id.* at ¶ 6.

63. ~~56.~~ Where Dr. Nolan developed any “invention, improvement, discovery, process, formula, technique, method, trade secret, or other intellectual property” (collectively, “Inventions” or “Invention”) while performing services under the Consultant Agreement, he agreed to “promptly and fully disclose” any Invention to Fluidigm. *Id.* at ¶ 7. And Dr. Nolan agreed to assign his rights to all such Inventions to Fluidigm. *Id.*

64. ~~57.~~ The Nolan Consulting Agreement also contained a confidentiality provision requiring Dr. Nolan to, in part, “not disclose, directly or indirectly, [Fluidigm’s confidential information] to any third person or entity” *Id.* at ¶ 8.3.

65. ~~58.~~ Dr. Nolan worked under the Nolan Consulting Agreement with Fluidigm for over two and one-half years, until they mutually agreed to terminate the Nolan Consulting

Agreement effective on December 31, 2016. At the time of the termination of the Nolan Consulting Agreement, Dr. Nolan understood, knew of, and Fluidigm reminded him of his confidentiality obligations owed to Fluidigm.

66. ~~59.~~ On September 16, 2014, shortly after Dr. Nolan entered into the Nolan Consulting Agreement, Dr. Nolan together with Drs. Angelo, Bendall, and Feinberg founded IONpath.

67. ~~60.~~ On information and belief, and while Dr. Nolan consulted with Fluidigm, IONpath and Dr. Nolan began working on directly competing technologies, as well as commercializing products, for pathology applications, including, eventually, IONpath's infringing "MIBIScope" technology.

B. Dr. Sean Bendall

68. ~~61.~~ Dr. Sean Bendall co-founded IONpath in September 2014 and currently sits on its Board of Directors. Prior to that time, Fluidigm retained Dr. Bendall to serve as a Consultant. Specifically, Fluidigm and Dr. Bendall entered into a Consulting Agreement dated April 26, 2014 and again on April 26, 2015 ("Bendall Consulting Agreements").

69. ~~62.~~ Pursuant to the Bendall Consulting Agreements, Fluidigm retained Dr. Bendall "to provide the following services: consulting services relating to labeling of biological samples and conjugation of biomolecules (including but not limited antibodies and other affinity reagents) with metal isotopes for use in inductively-coupled plasma (ICP) based biological assays including, but not limited to, the analysis of single-cells, biological extracts, homogenates, and fluids." Bendall Consulting Agreements at Ex. A.

70. ~~63.~~ Dr. Bendall agreed that he “will not, during or subsequent to the term of this Agreement, use the Company’s Confidential Information for any purpose whatsoever other than the performance of the Services on behalf of the Company or disclose the Company’s Confidential Information to any third party.” *Id.* at ¶ 2(b).

71. ~~64.~~ Dr. Bendall disclosed that he was “simultaneously and principally employed by and/or associated with Stanford University.” *Id.* at ¶ 3(e). Dr. Bendall certified that “[e]xcept for Consultant’s obligations to its fulltime employers,” he “has no outstanding agreement or obligation that is in conflict with any of the provisions of this Agreement or that would preclude Consultant from complying with the provisions hereof, and further certifies that Consultant will not enter into any such conflicting agreement during the term of this Agreement.” *Id.* at ¶ 4.

72. ~~65.~~ The Bendall Consulting Agreements provide that “Consultant is free to perform work as a consultant or employee for any other entity and/or person provided that such engagement does not create a conflict of interest with Consultant’s obligations to Company.” *Id.* at ¶ 7(b).

73. ~~66.~~ The Bendall Consulting Agreements were to expire on April 25, 2016 unless agreed otherwise in writing by both parties. *Id.* at ¶ 5(a). Dr. Bendall and Fluidigm extended the term of the Bendall Consulting Agreements twice to April 25, 2018.

74. ~~67.~~ On information and belief, and while Dr. Bendall consulted with Fluidigm, IONpath and Dr. Bendall began commercializing products for pathology applications, including, eventually, IONpath’s infringing “MIBIScope” technology.

IV. IONPATH'S MARKETING AND SALE OF ITS INFRINGING TECHNOLOGY

75. ~~68.~~ By at least February 2018, on information and belief, IONpath began contacting Fluidigm's customers for the express purpose of convincing Fluidigm's customers to use Fluidigm's proprietary Maxpar® antibodies and related reagents with IONpath's ~~systems.~~ MIBIscope system.

76. IONpath's MIBIscope system is a specifically built mass cytometry system whose sole function is to analyze and image biomarkers within cellular structures through the use of technology expressly covered by the methods contained in Fluidigm's '104 and '386 Patents and the system described in Fluidigm's '698 Patent. Mass cytometry systems, such as employed by the infringing MIBIscope system, require the use of antibodies specifically designed to target biomarkers of interest within the sample being analyzed, which is the method described and claimed in the '386 Patent and the system in the '698 Patent. The antibodies themselves are linked to polymers with specific metal tags as reagents for purpose of this analysis, as described in the '104 Patent.

77. The creation of these special reagents and antibodies is difficult, time-consuming, and costly and working with multiple antibodies increases the chances of user error – although the benefit of being able to analyze a sample with multiple antibodies is one of the characteristics that makes this technology particularly useful and is one reason the methods of the '104 Patent and the '386 Patent, and the system of the '698 Patent, are valuable. As such, the reagents and antibodies used by mass cytometry systems are specifically created for that purpose and are not generic or common. The antibodies are selected and engineered for their specific affinity for

particular biomarkers of interest within a sample or cell. The selected antibodies described in the '104 Patent, for example, include those covalently linked to a particular type of polymer containing multiple binding sites for selected lanthanide tags. The combination of antibodies and lanthanide tags must be carefully and intentionally created or else any analysis of the created reagent will be unreliable. Fluidigm was the first, and the only company, that has commercially available, validated reagents and antibodies.

78. On information and belief, IONpath began using and offering its MIBIScope product for use and/or sale to potential customers as early as December 2017, prior to the official commercial launch of the product in November 2019. IONpath offered to sell the MIBIScope product to customers for approximately \$1,000,000.00 to \$1,400,000.00.

79. On information and belief, in 2017, IONpath first offered for sale and sold the MIBIScope product to researchers who were previously associated with Dr. Nolan's lab at Stanford University. Dr. Nolan's lab at Stanford University also acquired from IONpath and used a MIBIScope product prior the IONpath's official commercial launch.

80. At the time IONpath first began offering the infringing MIBIScope product and system for sale, prior to its full commercial launch in November 2019, IONpath did not have any of its own reagents or antibodies available for sale to its customers and potential customers. Thus, when IONpath was offering to sell and selling its MIBIScope product and system to customers in 2017, IONpath did so with the full expectation, knowledge, and intent that its customers and potential customers would necessarily purchase and use Fluidigm's Maxpar reagents and antibodies for use with the MIBIScope system, as Fluidigm's Maxpar reagents and

antibodies were the only products commercially available and validated that could be used with the MIBIScope system. On information and belief, IONpath did not offer for commercial sale any reagents or antibodies of its own until at least July 2019.

81. ~~69.~~ On or about February 7, 2018, Fluidigm expressly put IONpath on notice that by inducing ~~and~~, seeking ~~to convince~~, and convincing customers to use the Maxpar antibodies and related reagents with IONpath's infringing technology, IONpath was causing customers to breach the Sales and License Terms and Conditions ("Ts&Cs") each customer agreed to when they purchased and were using Fluidigm's proprietary Maxpar® antibodies and related reagents. See Ts&Cs at § 3.2.

82. ~~70.~~ Specifically, Fluidigm ~~identified, among others,~~ explained to IONpath that Fluidigm's customers had agreed ~~to~~, among other things, not to: ". . . (iv) use any Fluidigm consumables or reagents with any non-Fluidigm instrument, device or system." ~~Ts&Cs at § 3.2.~~ Id.

83. ~~71.~~ Fluidigm also ~~expressed its concern~~ expressly advised IONpath that Fluidigm was deeply concerned that IONpath sought to employ former Fluidigm consultants and employees to foster an environment where those employees and consultants would be pressured to breach their confidentiality obligations owed to Fluidigm.

84. ~~72.~~ While IONpath denied any wrongdoing in two letters it sent to Fluidigm in February and March 2018, ~~Fluidigm later~~ Dr. Nolan's lab at Stanford University was at the same time ordering Fluidigm Maxpar products for use with the MIBIScope method and system. Specifically, Dr. Nolan's lab placed approximately 10 orders of Maxpar® X8 Multimetal

Labeling Kits as well as 8 Maxpar® X8 Antibody Labeling Kits with Fluidigm between February 2018 and September 2018 for use with the MIBIScope method and system.

85. Dr. Nolan's lab received sales quotes from Fluidigm that expressly incorporated and included copies of the Ts&Cs. After Dr. Nolan's lab accepted the terms of sale, they placed orders for Fluidigm's Maxpar products with Fluidigm. Fluidigm then sent confirmations of the orders to Dr. Nolan's lab attaching and incorporating the Ts&Cs – and also included a direct electronic link to the Ts&Cs.

86. Even after Fluidigm expressly advised IONpath of the contractual provisions associated with its Maxpar products, and even though the Dr. Nolan lab accepted, agreed to be bound by, and received multiple copies of the Ts&Cs, Fluidigm learned that IONpath's founders, Drs. Bendall and Angelo, ~~even after the warning from Fluidigm~~ also associated with Stanford, submitted a paper to the *Cell* journal on April 16, 2018, that admitted to improperly using Fluidigm's Maxpar X8 Antibody labeling kit as a Critical Commercial Assay for IONpath's technology, in direct violation of the Ts&Cs.

87. ~~73.~~ Not only did IONpath's founders' admissions in the paper ~~admit~~ confirm that IONpath knew that it and its founders breached the Ts&Cs, but the paper also expressly encouraged Fluidigm's customers and future customers to similarly breach their contractual obligations with Fluidigm, the Ts&Cs, by improperly using Fluidigm antibodies and related reagents with non-Fluidigm systems.

88. If blatantly ignoring Fluidigm's demand to cease and desist from breaching and inducing others to breach Fluidigm's Ts&Cs was not enough, after Fluidigm served IONpath

with both the original Complaint and First Amended Complaint, IONpath founders Drs. Angelo and Bendall co-authored another article, which published on January 17, 2020 (the “2020 Article”), which states, “[a]ntibodies were conjugated to heavy-metal ions with MaxPar (Fluidigm) or MIBItag (IONpath) reagents using an optimized conjunction protocol . . .” and used with “MIBI-TOF,” IONpath’s MIBIScope system. 2020 Article, attached as Exhibit G, at p. 41. Drs. Angelo and Bendall authored the 2020 Article as representatives of Stanford. Drs. Angelo and Bendall (as founders of IONpath) knew that using and/or causing Stanford to use Fluidigm Maxpar reagents with an IONpath MIBIScope was intentionally resulting in Stanford breaching its agreements with Fluidigm as reflected in the Ts&Cs. Moreover, by publishing articles that would cause third-parties to believe they too could use the MIBIScope with Maxpar reagents would, and did, induce Fluidigm’s customers to breach their Ts&Cs.

89. As of January 31, 2020, at least seven additional entities that acquired IONpath’s MIBIScope also ordered, after September 2018, antibodies and related reagents from Fluidigm, and all eight or more entities were and are bound by the same contractual prohibitions. Those entities include: Dana-Farber Cancer Institute; University of Colorado, Denver; University of Minnesota; Mount Sinai Health System; University of Texas MD Anderson Cancer Center; University of California, San Francisco; and Bluebird Bio.

90. All eight of these Fluidigm customers agreed to be bound by the Ts&Cs and, on information and belief, have breached and continue to breach the Ts&Cs by improperly using Fluidigm antibodies and reagents with the infringing MIBIScope, as promoted, marketed, encouraged, and advertised by IONpath.

91. On information and belief, the entities that purchased, leased, and used IONpath's infringing MIBIScope would not have done so if they could not use the MIBIScope due to a lack of available, validated, reagents and antibodies. Instead, these entities would have purchased Fluidigm's Hyperion system, or another Fluidigm mass cytometry system, and would have used Fluidigm's reagents and antibodies consistent with their contractual obligations under the terms and conditions of the Ts&Cs. Put another way, but for IONpath's encouragement for its actual and potential customers of the MIBIScope to use Fluidigm's antibodies and reagents in breach of the Ts&Cs, IONpath could not have sold the MIBIScope to these customers and these customers likely would have purchased Fluidigm's Hyperion system, or another Fluidigm mass cytometry system, instead.

IONpath announces its infringing MIBIScope technology in 2018.

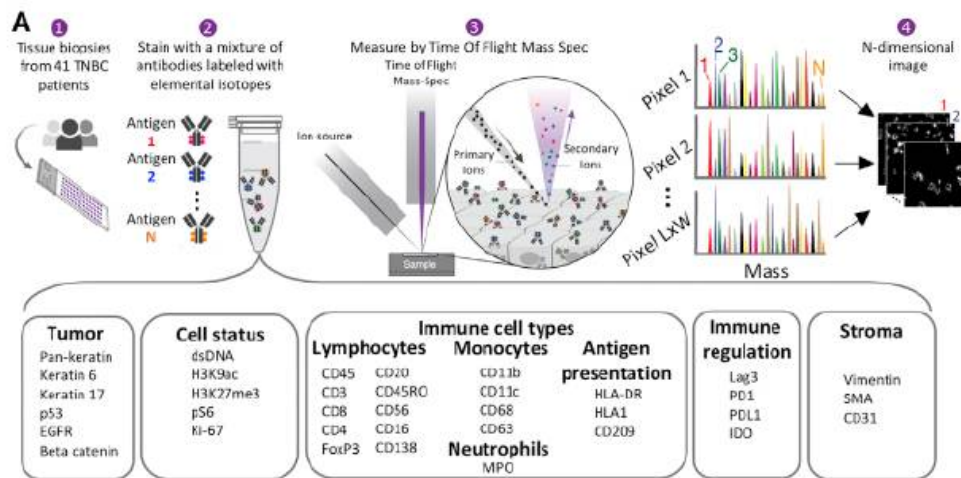
92. ~~74.~~ In the September 6, 2018 press release ("2018 Press Release"), IONpath celebrated the publication of Drs. Bendall and Angelo's work in the journal *Cell* detailing the performance of its MIBI technology and improper use of the Fluidigm antibodies and related reagents.

93. ~~75.~~ The 2018 Press Release claimed that the MIBI technology was invented in Dr. Nolan's lab and subsequently developed by Drs. Bendall and Angelo. The 2018 Press Release reveals that IONpath's MIBI technology "uses secondary-ion mass spectrometry (SIMS), . . . to image antibodies tagged with monoisotopic metal reporters, permitting 40+ proteins to be simultaneously measured.²²" which describes, generally, the method set forth in at least exemplary claim 9 of the '386 Patent.

94. ~~76.~~ The 2018 Press Release also asserted that IONpath was piloting its “MIBIScope” with “research institutes and biopharmas . . . in which high-fidelity multiplexed imaging data is needed.”

95. ~~77.~~ The IONpath *Cell* publication, titled “A Structured Tumor-Immune Microenvironment in Triple Negative Breast Cancer Revealed by Multiplexed Ion Beam Imaging” (the “2018 Article”), used “multiplexed ion beam imaging by time-of-flight (MIBI-TOF)” to quantify in position expressions of 30+ proteins from certain tissues.

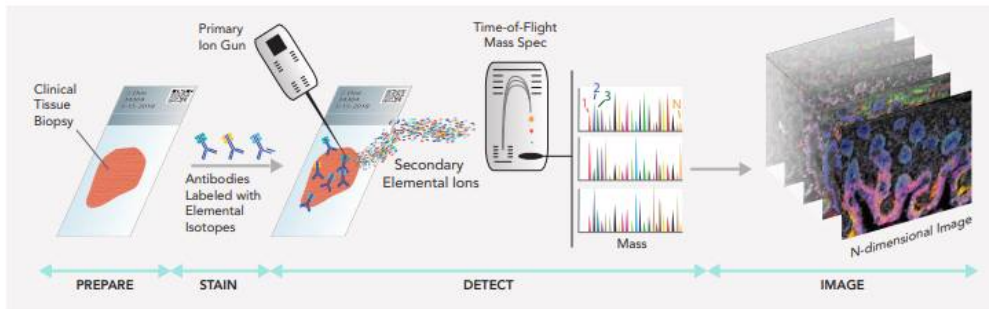
96. ~~78.~~ The 2018 Article describes the method by which the authors conducted the study; namely, taking tissue biopsies and staining them with “a mixture of antibodies labeled with elemental isotopes.” Once stained, the authors’ methodology called for raster-scanning the tissues with an ion beam resulting in the generation of secondary elemental ions, which the authors proceeded to analyze doing time-of-flight mass spectrometry. As such, the 2018 Article, like the 2018 Press Release, described for its audience implementing the method set forth in the ’386 Patent: from a sample containing “tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal”; to raster-scanning with an ion beam – or “vaporizing, atomizing, and ionizing” the target cells; and finally, analyzing the “vaporized, atomized, and ionized” cells by time-of-flight mass spectrometry.



See 2018 Article at Figure A1 describing [the infringing](#) MIBI-TOF workflow.

[97.](#) ~~79.~~ The 2018 Article explicitly references certain authors' association with IONpath: "M.A. and S.C.B. [Dr. Bendall] have patents relating to MIBI technology and are board members, shareholders, and consultants in Ionpath Inc."

[98.](#) ~~80.~~ At or about the time the 2018 Article published, IONpath posted on its website a brochure for ~~its~~ [the](#) MIBIScope I [\(the "2018 Brochure"\)](#), as discussed above, describing how it works in much the same manner. ~~The brochure~~ [making it a system that infringes on the '698 Patent. The 2018 Brochure](#) advertises that "[t]he MIBIScope system uses Secondary Ion Mass Spectrometry (SIMS) and enables simultaneous imaging of 40+ markers" where "tissue samples are raster scanned with a particle ion beam" and "detected via TOF mass spectrometry."²² [which, generally, describes a system that infringes Fluidigm's '698 Patent.](#)



99. 81. The ~~brochure~~ [2018 Brochure](#) also included images that, on information and belief, IONpath generated with its MIBIScope using Fluidigm's Maxpar antibodies and related reagents ~~in~~ [reflecting a](#) further breach of the Ts&Cs.

100. 82. IONpath's website ~~further~~ advertises "MIBI™ Reagents for HIGH Multiplex Imaging" and has distributed a brochure describing "isotopically conjugated antibodies" and antibody conjugation kits using antibodies conjugated to lanthanides. IONpath's Safety Data Sheets for MIBItag Conjugation Kits, available on the IONpath website, describe these materials as including lanthanides and polymer components. [Similar to Fluidigm's reagents and antibodies, IONpath's MIBItags are specially designed and created solely for use as a part of its infringing mass cytometry system and serve no other purpose except for use with such systems.](#)

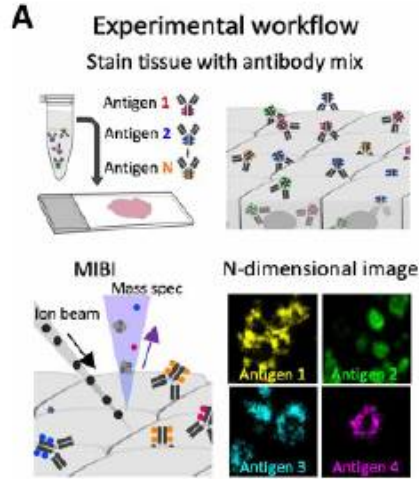
101. 83. IONpath's website also advertises its Pharma Partnership service - an in-house analysis method for customers where IONpath conducts "tissue staining, imaging and scanning:" [using the infringing mass cytometry method and system.](#)

102. 84. On September 18, 2018, IONpath announced that it planned to launch a commercial version of ~~its~~ [the](#) infringing technology in 2019.

103. ~~85.~~ Even though previously warned in February 2018, IONpath's founders' blatant breach of the Ts&Cs, and inducement and encouragement ~~to~~of other Fluidigm customers to engage in the same wrongful conduct, resulted in Fluidigm sending another letter to IONpath, on September 24, 2018, seeking IONpath's commitment to refrain from improper and tortious conduct.

104. ~~86.~~ In addition, in Fluidigm's September 2018 letter, Fluidigm gave ~~notice to~~ IONpath notice of Fluidigm's then recently issued '104 Patent, ~~of which IONpath confirmed it was aware.~~

105. Despite having further notice of the '104 and '386 Patents via service of the original Complaint on September 23, 2019, and further notice of the '698 Patent via service of the First Amended Complaint on October 11, 2019, IONpath has continued to use the infringing system and method, offer it for sale, and advertise the commercial availability thereof, including in the IONpath *Science Advances* publication titled "MIBI-TOF: A Multiplexed Imaging Platform Relates Cellular Phenotypes and Tissue Structure" (the "2019 Article"), which describes results obtained with MIBI-TOF instrumentation – which is the system infringing the '698 Patent – and indicates that "[c]urrent commercial MIBI-TOF instrumentation is being manufactured by IonPath Inc. (Menlo Park, CA)." Attached as Exhibit F.



See 2019 Article at Figure A describing MIBI-TOF workflow.

106. Through the 2019 Article, and other conduct, IONpath expressly markets, offers for sale, and encourages customers and potential IONpath customers to purchase a system IONpath knows infringes on the '698 Patent including, but not limited to, through implementation and infringement of the methods in the '386 and '104 Patents.

107. IONpath founder Dr. Bendall also co-authored a review in *Nature Reviews* titled “Immune Monitoring Using Mass Cytometry and Related High-Dimensional Imaging Approaches,” which originally published online on December 31, 2019 and was included in *Nature Reviews* for its February 2020 edition (the “2020 Review,” attached as Exhibit H). The 2020 Review details the significant similarities between MIBI and Fluidigm's Imaging Mass Cytometry (“IMC”). The 2020 Review explains, for example, that MIBI was developed for the sole purpose of analyzing samples stained with antibodies tagged with metal-isotopes through a method wherein the sample has secondary ions released through the use of an ion beam raster

scanned across the sample. The secondary ions are then passed through the detection system to complete the process, which is the method set forth in the '386 Patent.

108. IONpath, by having its founder Dr. Bendall publish the 2020 Review, continued to promote and encourage IONpath customers and prospective customers to infringe on the '698 Patent by using the MIBIScope and instructed them on how the MIBIScope functioned in employing the methods in the '386 and '104 Patents.

V. IONPATH'S IMPROPER AND INFRINGING COMMERCIAL ACTIVITY

109. 87. In February 2019, Fluidigm learned that IONpath had contacted at least one of Fluidigm's customers, on information and belief, in an effort to demonstrate IONpath's MIBIScope and reagents, and teaching them how to infringe upon the '386 and '104 Patents, and to sell the infringing technology, which would be the system infringing on the '698 Patent.

110. 88. On information and belief, by August 2019, IONpath ~~has~~had sold at least six, and possibly more, of its infringing MIBIScopes (and potentially reagents) to various ~~institutions.~~ entities. In the month prior, IONpath ~~has~~had also begun commercially ~~marketed~~marketing the MIBItags labeling reagents on its website and brochures.

111. By January 31, 2020, even with full knowledge of how the MIBIScope infringes Fluidigm's Patents based upon, at least, the allegations in the Original and First Amended Complaints in this lawsuit, IONpath has sold at least four additional infringing MIBIScopes to various entities.

112. Despite service of the Original and First Amended Complaints on September 23, 2019 and October 11, 2019, respectively, IONpath went ahead with the announcement of the commercial launch of the MIBIScope on their website on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the **MIBIScope™ System**, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

See <https://www.ionpath.com/news/> (attached as Exhibit D). IONpath’s 2019 formal commercial launch press release (“2019 Press Release”) offers for sale and urges third-parties to purchase the infringing MIBIScope system. The 2019 Press Release also advertises that IONpath “is showcasing the [infringing] platform at the Society for Immunotherapy of Cancer Annual Meeting (SITC)” held November 6, 2019 through November 10, 2019 (the “2019 SITC Meeting”).

113. At the 2019 SITC Meeting, with full knowledge of the allegations in this lawsuit, IONpath continued to offer for sale, market, and push potential customers to purchase its infringing MIBIScope by, among other activities, placing MIBIScope brochures with the header “now commercially available” in all conference registration bags, by making several presentations relating to use of the infringing MIBIScope, and by providing an informational booth. At IONpath’s booth, on information and belief, IONpath explained to potential customers on how to infringe the methods set forth in the '104 and '386 Patents by use of the MIBIScope. See Exhibit E.

114. Several other research institutions attended and presented research at the 2019 SITC Meeting that was conducted using IONpath's infringing MIBIScope, including the Dana-Farber Cancer Institute, Stanford University, and the University of Colorado, Denver. IONpath promoted its customers' presentations of this research at the 2019 SITC Meeting as a part of their November 5, 2019, formal commercial launch. IONpath touted its own attendance at the 2019 SITC Meeting, and that of three of its customers, to further market, advertise, offer for sale, and entice third-parties to purchase the infringing MIBIScope, all with knowledge of the MIBIScope system infringing the '698 Patent based upon IONpath's undisputable knowledge of the allegations in Fluidigm's First Amended Complaint.

115. At the 2019 SITC Meeting, IONpath founder, Dr. Angelo, presented at a lunch symposium explaining and recommending to approximately 60 attendees the infringing use of the MIBIScope. IONpath CEO, Dr. Fienberg, moderated the presentation. Dr. Angelo's portion of the presentation described the MIBIScope's specifications and explained the MIBIScope's function. As explained by Dr. Angelo, which is consistent with IONpath's advertisements of the MIBIScope, the sole function of the MIBIScope is the imaging of biomarkers using antibodies with metal tags wherein the metal tags are ionized and then detected using time of flight mass spectrometry. In other words, the MIBIScope mass cytometry system is designed and advertised to infringe the patented methods in the '104 and '386 Patents as well the system of the '698 Patent.

116. Dr. Angelo's co-presenters from Dana-Farber Cancer Institute and University of Colorado, Denver, also detailed how IONpath representatives offered technical support to assist

the co-presenters institutions in using the MIBIScope by teaching them how to implement and perform the methods claimed in the '104 and '386 Patents. The presenter from Dana-Farber Cancer Institute discussed his work using the infringing MIBIScope including that he was now analyzing samples of up to 27 biomarkers by implementing the methods in the '104 and '386 Patents as well as using the MIBIScope as a system infringing on the '698 Patent.

117. The presenter from the University of Colorado, Denver, discussed how she had used the MIBIScope to expand her work and, on the University's website (<http://www.ucdenver.edu/academics/colleges/medicalschoo/programs/immunology-immunotherapy/HIMSR/HIMSRratesandservices/Pages/Imaging.aspx>), details that the University is using the MIBIScope to “simultaneously distinguish over 40 markers (depends on the number of metals) with high sensitivity” and that the University has a “27-marker panel.” The University's website and presentation confirm that they are implementing the methods claimed in the '104 and '386 Patents as well as using the MIBIScope as a system infringing on the '698 Patent.

118. IONpath's cavalier attitude in continuing with the 2019 Press Release and actively participating in the 2019 SITC Meeting – with full knowledge of Fluidigm's Patents and the allegations in the First Amended Complaint – verifies its egregious disregard for Fluidigm's intellectual property rights and IONpath's infringement of those rights.

119. Similarly, in addition to inducing Stanford to breach the Ts&Cs, Drs. Bendall and Angelo's participation in the 2020 Article demonstrates how they were teaching other researchers at Stanford methods that infringe on the claims of the '104, '386 and '698 Patents.

120. In particular, Drs. Bendall and Angelo explain in the 2020 Article that they made “use of heavy metal-conjugated antibodies that are quantified by TOF MS, thus allowing highly multiplexed, single-cell and imaging assays,” using “the recently developed multiplexed ion beam imaging (MIBI-TOF) platform,” (and citing to a 2019 Article by Keren in *Science Advances* for the MIBI-TOF platform, which 2019 Article discloses implementation of MIBI-TOF using “commercial MIBI-TOF instrumentation ... being manufactured by IonPath Inc.”). Drs. Bendall and Angelo further explain that the heavy metal-conjugated antibodies that were used included “MaxPar (Fluidigm) or MIBItag (Ionpath) reagents,” and thus, yet again, describe a method and system that clearly infringe on Fluidigm’s ‘386 Patent and ‘698 Patent.

121. Drs. Bendall and Angelo further detail in the 2020 Article the conjugation of antibodies with the Maxpar or MIBItag reagents and washing, detailing exactly how to use the reagents: “For conjugations using MaxPar reagents, metal chelation was performed by adding metal solutions ... to chelating polymers and incubating Metal-loaded polymers were washed twice using a 3 kDa MWCO microfilter” Drs. Bendall and Angelo further describe staining a sample with the conjugated antibodies and, “[b]efore acquisition, samples were washing once in CSM and twice in ddH₂O and filtered.” Unmistakably, IONpath’s founders were detailing not only how to use the MaxPar and MIBItag reagents, but also describe a method that infringes a claimed method of the ‘104 Patent.

122. With full knowledge of the allegations in the First Amended Complaint served on IONpath more than two months earlier, IONpath’s founders proceeded with the publication of

the 2020 Article with further teachings and instructing third-parties on how to infringe on the methods in the '386 and '104 Patents.

123. In addition to offering for sale and selling its MIBI System, on February 11, 2020, IONpath “announce[d] the launch of a dedicated service business providing access to” IONpath’s infringing “MIBIScope™ multiplexed imaging platform and its team of experts to support pharmaceutical and biotechnology companies working in immune-oncology.” IONpath’s February 11, 2020 press release (the “2020 Service Announcement”) admitted that IONpath had surreptitiously offered this service “to leading academic and pharmaceutical organizations as part of an Early Access Program.” The 2020 Service Announcement proclaimed that IONpath wanted to “partner” with customers – and had previously done so – to use the infringing MIBIScope for customers. The 2020 Service Announcement makes clear that IONpath has and will implement the infringing methodologies of the '386 and '104 Patents for customers.

124. ~~89.~~ Fluidigm has been harmed by IONpath’s flagrant unauthorized use and egregious continued infringement of Fluidigm’s patented methods and technologies.

COUNT I

INTENTIONAL INTERFERENCE WITH CONTRACTUAL RELATIONS

125. ~~90.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

126. ~~91.~~ Fluidigm ~~requires that its customers~~ enters into contracts with its customers for Maxpar® antibodies and reagents where its customers expressly agree to reasonable restrictions.

on the use of the Maxpar® antibodies ~~agree to certain~~(the Ts&Cs). The Ts&Cs contain provisions through which Fluidigm’s customers agree to not “use any Fluidigm consumables or reagents with any non-Fluidigm instrument, device or system.” Ts&Cs at § 3.2.

127. Fluidigm provides its customers with a copy of the Ts&Cs when it sends the customers a sales quote for the desired products. The sale quote specifically incorporates the Ts&Cs in the terms of sale. When the customer agrees to purchase Fluidigm’s products, Fluidigm sends the customer a sales confirmation expressly incorporating the Ts&Cs and, again, attaching the Ts&Cs. Fluidigm’s Ts&Cs are a binding part of each and every sale Fluidigm makes with its customers for the sale of its Maxpar® antibodies.

128. 92. Upon~~On~~ information and belief, IONpath ~~had~~ received, in whole or in part, Fluidigm’s Ts&Cs no later than February ~~2018~~2018, and knew that Fluidigm’s customers ~~could not~~ ~~“use~~ were contractually prohibited from using “any Fluidigm consumables or reagents with any non-Fluidigm instrument, device or system.” Moreover, in February 2018, Fluidigm gave IONpath express notice that using (or encouraging others to use) Fluidigm’s antibodies and reagents with a non-Fluidigm system violated the Ts&Cs.

129. 93. In complete disregard for Fluidigm’s contracts with its customers and the Ts&Cs, IONpath ~~continued to encourage~~intentionally induced Fluidigm’s customers, described above, to breach the Ts&Cs by promoting the use of Fluidigm’s antibodies and related reagents with IONpath’s technology through, among other means: publications, brochures, press releases, and direct contact.

130. 94. IONpath's MIBIScope would not function if the MIBIScope-owner lacked access to the specialized and custom designed antibodies and reagents that could work with the MIBIScope. IONpath did not offer antibodies and reagents for sale until July 2019, even though IONpath had already sold the MIBIScope product to its customers. Prior to July 2019, Fluidigm's Maxpar antibodies and reagents were the only such antibodies and reagents commercially available and specifically designed to work with these types of mass cytometry systems.

131. IONpath's actions, especially after receiving notice from Fluidigm, were intentional with IONpath's full knowledge that it would result in Fluidigm's customers breaching their ~~contracts with~~ contractual obligations with and to Fluidigm.

132. As of January 2020, at least eight of IONpath's customers purchased Fluidigm's antibodies and reagents – and entered into contracts with Fluidigm where they accepted and agreed to be bound by Fluidigm's Ts&Cs – for use with an IONpath MIBIScope and in breach of the Ts&Cs. IONpath induced at least these eight IONpath customers to breach the Ts&Cs by encouraging the eight customers to purchase and use Fluidigm's reagents and antibodies in direct breach of the Ts&Cs, and promoting and publishing results that IONpath's customers could expect to obtain if it purchased and used a MIBIScope with Fluidigm's reagents and antibodies.

133. IONpath's MIBIScope customers would not have purchased a MIBIScope had IONpath not induced them into breaching Fluidigm's Ts&Cs by using Fluidigm reagents and antibodies with the MIBIScope – as the customers would not have been able to use the MIBIScope without Fluidigm's reagents and antibodies. Instead, on information and belief, the

MIBIscope customers -- intent on purchasing a functioning mass cytometry system -- would have purchased a mass cytometry system from Fluidigm.

134. ~~95.~~ IONpath's intentional interference with Fluidigm's contracts with its customers has harmed Fluidigm by ~~encouraging~~ causing Fluidigm's customers to engage in the unauthorized use of Fluidigm's Maxpar antibodies and related reagents in manners that breach the Ts&Cs and result in ~~unsafe and~~ untested and unvalidated results and uses.

135. ~~96.~~ IONpath's intentional interference with the Ts&Cs is a substantial factor in causing Fluidigm's loss of business opportunities because IONpath has sold at least eight MIBIsopes to customers who IONpath encouraged and intended would use the MIBIscope with Fluidigm's antibodies and reagents, in potentially untested and unvalidated manners, as opposed to purchasing a Fluidigm system and using Fluidigm's antibodies and reagents in a validated and tested manner.

COUNT II
DIRECT PATENT INFRINGEMENT
(The '386 Patent)

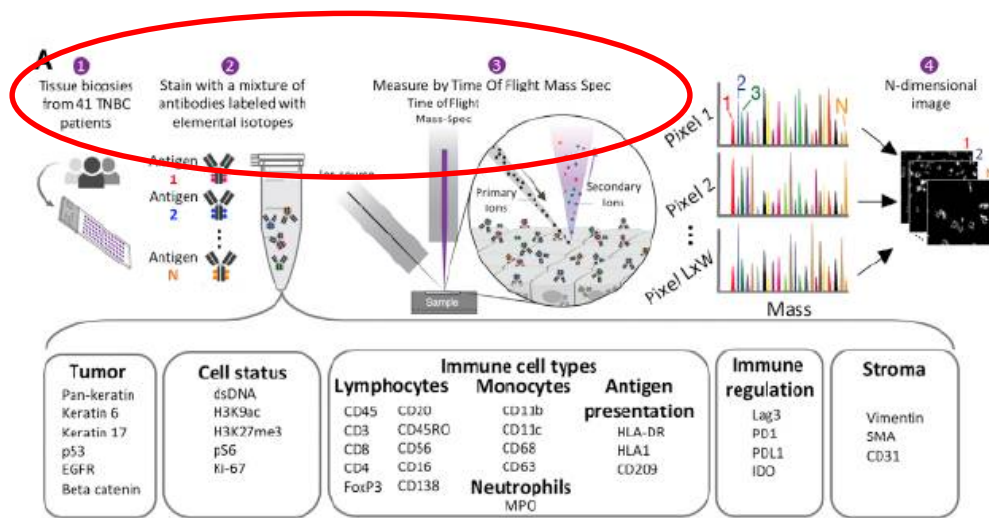
136. ~~97.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

137. ~~98.~~ On January 15, 2019, the Patent Office duly and legally issued the '386 Patent.

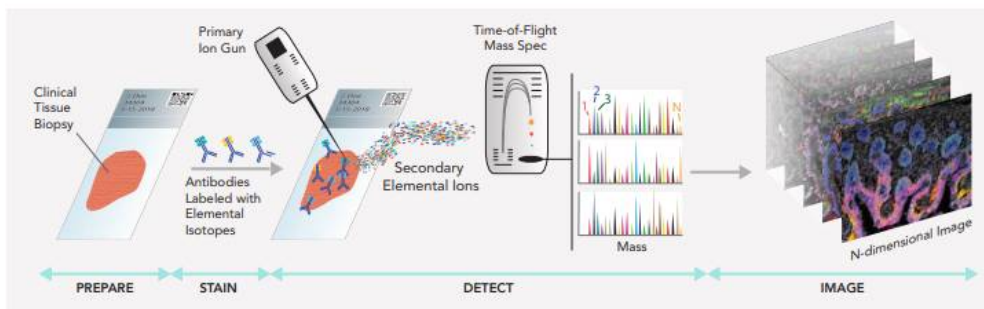
138. ~~99.~~ Fluidigm is the owner, by assignment, of all right, title, and interest in and to the '386 Patent, including, but not limited to, the right to recover damages for past and future infringement.

139. ~~100.~~ IONpath has been and is directly infringing, literally and/or under the doctrine of equivalents, the '386 Patent in violation of 35 U.S.C. § 271 by, among other things, using systems and methods for the analysis of a single cell, including, but not limited to, staining by a mixture of antibodies tagged with elemental tags of lanthanide or noble metal, ionizing, and then analyzing using mass spectroscopy and time of flight analysis to detect the signal of the ionized elemental tags, which methods are covered by one or more of the claims of the '386 Patent, including, but not limited to, exemplary claim ~~1.9.~~

140. ~~101.~~ As IONpath published in the 2018 Article, IONpath constructed a “purpose-built instrument” that implements “a method that uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” combined with “time-of-flight mass spectrometry” This is further evidenced by, among other things, the summary IONpath included in the 2018 Article at Figure 1A:



141. ~~102.~~ IONpath's website also confirms in a brochure that its MIBIScope I is the "purpose-built" machine that ~~implements~~serves no other purpose except to implement Fluidigm's patented method:



142. IONpath announced the formal commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the **MIBIScope™ System**, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

See <https://www.ionpath.com/news/>

143. ~~103.~~ IONpath has also commercialized MIBItags that are isotopically labelled antibodies that implement Fluidigm's patented method when combined with IONpath's MIBIScope. IONpath has used and advocated use of ~~these~~its MIBItags in combination with ~~their~~its IONpath instruments on ~~their~~its website, and has published results obtained with the MIBIScope and identifying MIBItags as the labeling reagents (in the 2018 Article referred to above, *see* Supplementary Material, page e1, Critical Commercial Assays).

STAR★METHODS**KEY RESOURCES TABLE**

Critical Commercial Assays

| | | |
|---|---------------------|----------------|
| Maxpar X8 Antibody labeling kit | Fluidigm | Cat#2011XXX |
| MIBitag Conjugation Kit | IONpath | Cat#600XXX |
| ImmPRESS UNIVERSAL (Anti-Mouse/Anti-Rabbit) IgG KIT (HRP) | Vector Laboratories | Cat#MP-7500-15 |
| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

144 ~~104~~. On information and belief, at least with respect to the subject matter of the methods disclosed and claimed in the ‘386 Patent, the use of the “purpose-built” MIBIscope for performing mass spectrometry analysis directly infringes at least exemplary claim ~~19~~ of the ‘386 Patent.

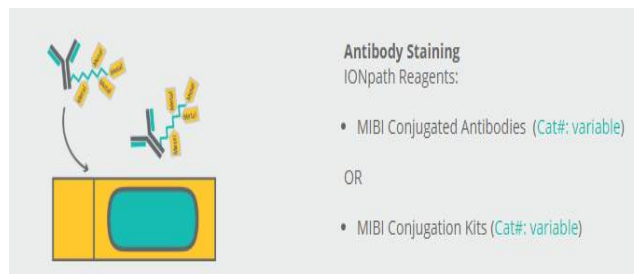
145 ~~105~~. A chart setting out the elements of exemplary claim ~~19~~ of the ‘386 Patent (and including the elements of claim 1, from which claim 9 depends), and certain, but not all, representative corresponding infringing activities of IONpath, is below.

‘386 Patent

| Claim Element | IONpath Activities |
|--|---|
| 1. A method of sequentially analyzing single cells by mass spectrometry, comprising: | <p>IONpath’s MIBIscope <u>MIBI technology system (the “MIBI System”), which include the MIBIscope in combination with IONpath’s MIBitag reagents or other suitable reagent (e.g. Fluidigm’s Maxpar reagents).</u> performs a method of sequentially analyzing single cells by mass spectrometry.</p> <p>https://www.ionpath.com/mibi-technology/</p> <p>MIBI™ technology (Multiplexed Ion Beam Imaging) uses Secondary-Ion Mass Spectrometry (SIMS), a type of mass spectrometry traditionally used in the semiconductor industry, to image antibodies tagged with monoisotopic metal reporters.</p> <p>This unique technology enables:</p> <ul style="list-style-type: none"> • Visualization of 40+ markers simultaneously • Imaging at the sub-cellular resolution • Detection of low abundance proteins • Rescanning of slides at multiple resolutions <p>https://web.stanford.edu/group/nolan/technologies.html</p> <p>Multiplexed ion beam imaging (MIBI) allows analyzing up to 100 targets</p> |

| | |
|---|---|
| | <p>simultaneously over a five-log dynamic range in a way similar to CyTOF, but in addition to measuring protein levels on individual cells, it also provides the information about cell morphology and localization.</p> <p><u>“Stationary tissue samples are raster-scanned with an ion beam and secondary elemental ions are generated.”</u></p> <p><u>Source: https://www.ionpath.com/mibi-technology/</u></p> |
| <p>providing a sample containing a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the tagged antibodies is specific for a different analyte, and wherein each of the tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal;</p> | <p>IONPath's <u>IONpath's MIBI System uses MIBItags</u> are used to create (or Fluidigm's Maxpar reagents) for providing a sample containing a plurality of tagged cells tagged with a plurality of tagged <u>different</u> antibodies, wherein each of the tagged antibodies is specific for a different analyte, and wherein <u>where</u> each of the tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal.</p> <p><u>https://www.ionpath.com/mibi-technology/</u></p> <p>STAIN: Tissue is stained with a mixture of validated antibodies with conjugated elemental reporters, in one single step.</p> <p>This unique technology enables:</p> <ul style="list-style-type: none"> • Visualization of 40+ markers simultaneously • Imaging at the sub-cellular resolution <p><u>2018 P106 Poster</u></p> <p>Samples were stained with a panel of 15 antibodies, each labeled with a specific metal isotope.</p> <p><u>https://www.ionpath.com/wp-content/uploads/2018/11/P106_IONpath_Ptacek_SITC-2018-2.pdf</u></p> |

<https://www.ionpath.com/reagents/>



SDS from <https://www.ionpath.com/antibody-conjugation-kit/>

| | |
|--------------------|---|
| Product identifier | MIBItag Conjugation Kit (Y) |
| Synonyms | None identified |
| Trade names | None identified |
| Chemical family | Lanthanide component Mixture - contains nitric acid and metal lanthanide Stabilization Buffer component Mixture - contains sodium azide Polymer component - contains diethylenetriaminepentaacetic acid |

2018 Cell Publication

<https://doi.org/10.1016/j.cell.2018.08.039>

STAR★METHODS

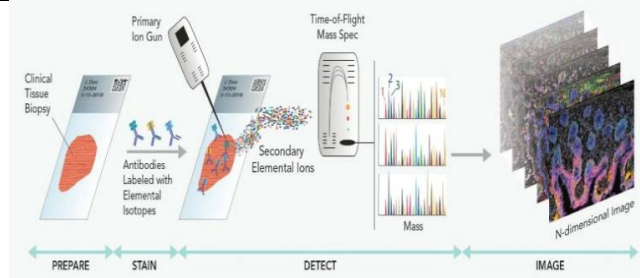
KEY RESOURCES TABLE

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| ImmPRESS UNIVERSAL (Anti-Mouse/Anti-Rabbit) IgG KIT (HRP) | Vector Laboratories | Cat#MP-7500-15 |
| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

vaporizing, atomizing, and ionizing multiple elemental tags from a single first cell of the plurality of tagged cells;

IONpath's [MIBI System](#) uses a [MIBIscope](#) ~~performs steps that~~ [meets the limitation](#) of vaporizing, atomizing, and ionizing multiple elemental tags from a single first cell of the plurality of tagged cells.

[IONpath's website shows vaporizing, atomizing, and ionizing using, for example, a primary ion gun.](#)



[Source: https://www.ionpath.com/mibi-technology/](https://www.ionpath.com/mibi-technology/)

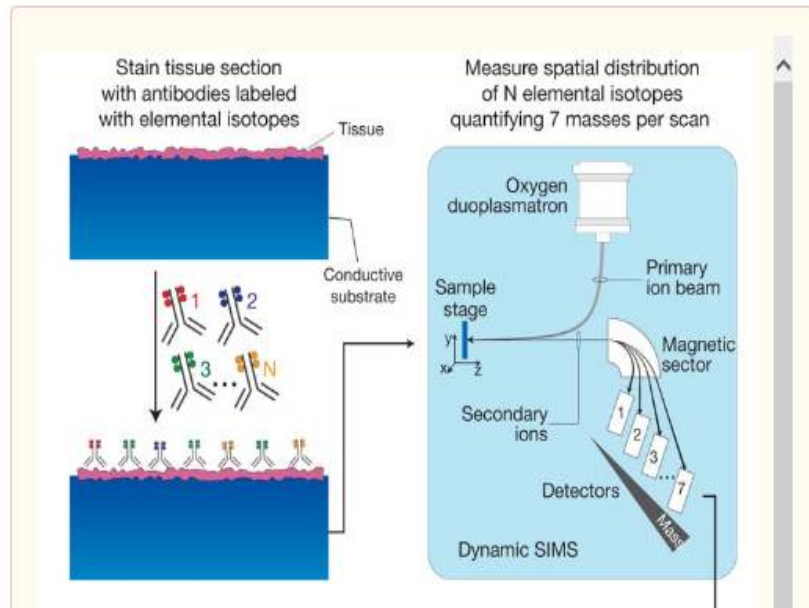
See also 2014 article with Nolan et al. on MIBI technique:
 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110905/>):

Results

Go to:

Performance assessment of MIBI

The workflow for MIBI is comparable to IF and IHC assays (Fig. 1). Instead of fluorophores or enzyme-conjugated reagents, biological specimens are incubated with primary antibodies coupled to stable lanthanides highly enriched for a single isotope (Fig. 1). Primary antibodies are combined in solution for simultaneous incubation with the specimen. The specimens prepared for MIBI are mounted in a sample holder and subjected to a rasterized oxygen duoplasmatron primary ion beam. As this ion beam strikes the sample lanthanide adducts of the bound antibodies are liberated as secondary ions. In this study, the secondary ions are subsequently analyzed via a magnetic sector mass spectrometer equipped with multiple detectors, permitting parallel detection of multiple lanthanide isotopes (mass-based reporters). The resultant data produces a two-dimensional map of the elemental distribution of each lanthanide, and thus each antibody and its corresponding epitope.



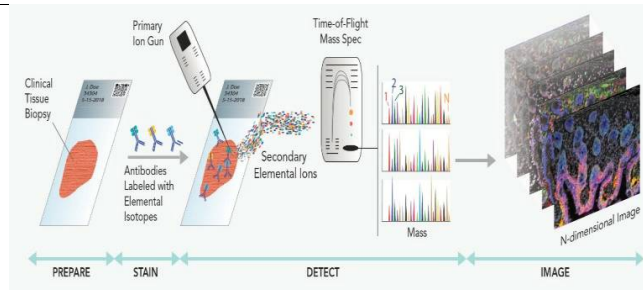
detecting, using mass spectrometry, the elemental composition of the first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell;

IONpath's **MIBI System** uses a **MIBIscope** that performs ~~steps of~~ detecting, using mass spectrometry, the elemental composition of the first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell .

<https://www.ionpath.com/mibi-technology/>

This unique technology enables:

- Visualization of 40+ markers simultaneously
- Imaging at the sub-cellular resolution



2018 Cell Publication

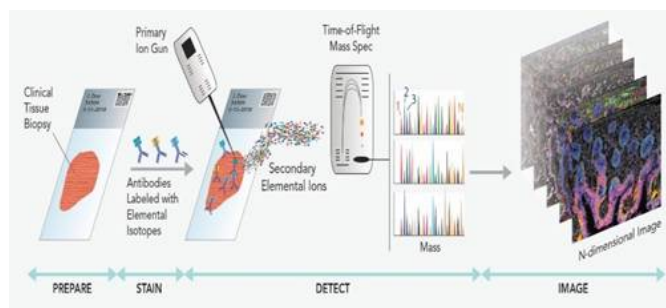
<https://doi.org/10.1016/j.cell.2018.08.039>

We have since constructed a purpose-built instrument that utilizes high brightness primary ion sources, novel ion extraction optics, and **time-of-flight mass spectrometry (TOF)** to increase channel multiplexing and decrease acquisition times 50-fold

vaporizing, atomizing, and ionizing multiple elemental tags from a single second cell of the plurality of tagged cells; and

IONpath's **MIBI System** uses a **MIBIscope** ~~performs steps~~ that meets the limitation of vaporizing, atomizing, and ionizing multiple elemental tags from a single second cell of the plurality of tagged cells.

“Stationary tissue samples are raster-scanned with an ion beam and secondary elemental ions are generated.”



Source: <https://www.ionpath.com/mibi-technology/>

See also 2014 article with Nolan et al. on MIBI technique:

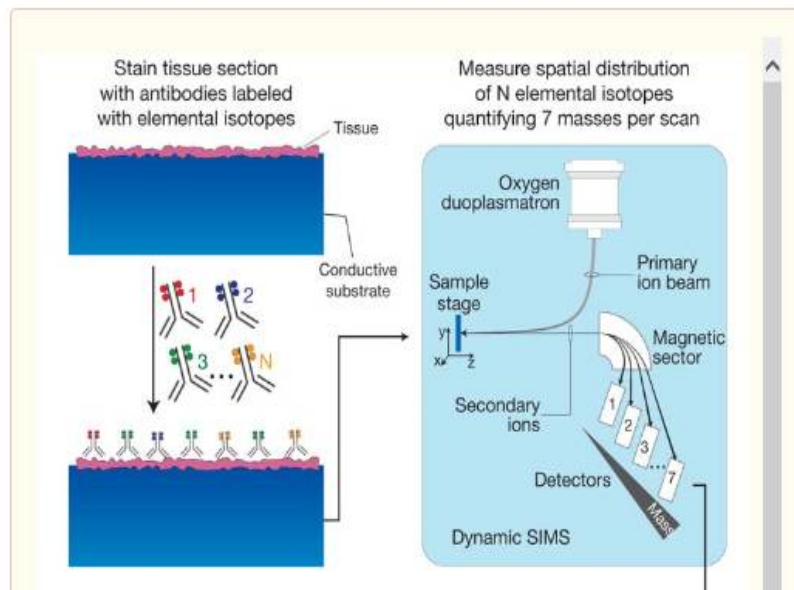
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110905/>):

Results

Go to:

Performance assessment of MIBI

The workflow for MIBI is comparable to IF and IHC assays (Fig. 1). Instead of fluorophores or enzyme-conjugated reagents, biological specimens are incubated with primary antibodies coupled to stable lanthanides highly enriched for a single isotope (Fig. 1). Primary antibodies are combined in solution for simultaneous incubation with the specimen. The specimens prepared for MIBI are mounted in a sample holder and subjected to a rasterized oxygen duoplasmatron primary ion beam. As this ion beam strikes the sample lanthanide adducts of the bound antibodies are liberated as secondary ions. In this study, the secondary ions are subsequently analyzed via a magnetic sector mass spectrometer equipped with multiple detectors, permitting parallel detection of multiple lanthanide isotopes (mass-based reporters). The resultant data produces a two-dimensional map of the elemental distribution of each lanthanide, and thus each antibody and its corresponding epitope.



detecting, using mass spectrometry, the elemental composition of the second cell by detecting a transient signal of the multiple

IONpath's [MIBI System](#) uses a **MIBIscope** ~~performs steps that meets the limitation~~ of detecting, using mass spectrometry, the elemental composition of the second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the second cell, wherein the transient signal associated with the first cell and the transient signal associated with the

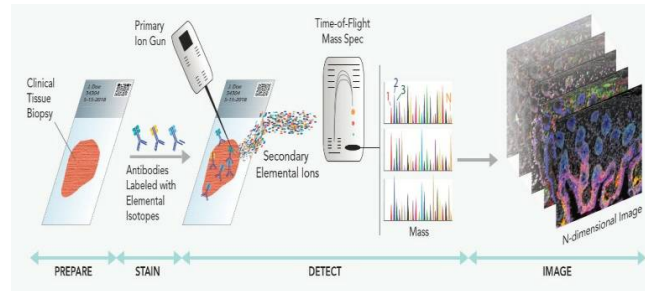
vaporized, atomized, and ionized elemental tags of the second cell, wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially.

second cell are detected sequentially.

<https://www.ionpath.com/mibi-technology/>

This unique technology enables:

- Visualization of 40+ markers simultaneously
- Imaging at the sub-cellular resolution



2018 Cell Publication

<https://doi.org/10.1016/j.cell.2018.08.039>

We have since constructed a purpose-built instrument that utilizes high brightness primary ion sources, novel ion extraction optics, and **time-of-flight mass spectrometry (TOF)** to increase channel multiplexing and decrease acquisition times 50-fold

9. The method of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope.

IONpath's MIBI System uses MIBItags (or Fluidigm's Maxpar reagents) to provide each of the plurality of tagged antibodies tagged with a distinct isotope.

IONpath's MIBItag conjugation kits allow users, for example, to choose an isotope for each respective antibody, while the conjugated antibodies are sold pre-tagged.

Conjugation Kits

Antibody conjugation kits provide the flexibility to label your antibody of interest with the metal you desire.

- Each kit provides 4 antibody conjugation reactions for labeling 100 ug of antibody

Source: <https://www.ionpath.com/antibody-conjugation-kit/>

Conjugated Antibodies

IONpath offers IHC validated antibodies to obtain optimal performance and save you time and money in extensive validation.

- Each lot of conjugated antibody is quality control tested by MIBI analysis of stained tissue microarray

Source: <https://www.ionpath.com/conjugated-antibodies/>

MIBI Technology allows users “to image antibodies tagged with monoisotopic metal reporters” with “[v]isualization of 40+ markers

MIBI™ Technology

MIBI™ technology (Multiplexed Ion Beam Imaging) uses Secondary-Ion Mass Spectrometry (SIMS), a type of mass spectrometry traditionally used in the semiconductor industry, to image antibodies tagged with monoisotopic metal reporters. This unique technology enables:

- Visualization of 40+ markers simultaneously
- Imaging at the sub-cellular resolution
- Detection of low abundance proteins
- Rescanning of slides at multiple resolutions

simultaneously[.]”

Source: <https://www.ionpath.com/mibi-technology/>

In IONpath webinars, the MIBIscope provides “single cell analysis and metal isotopes mass spectrometry.”

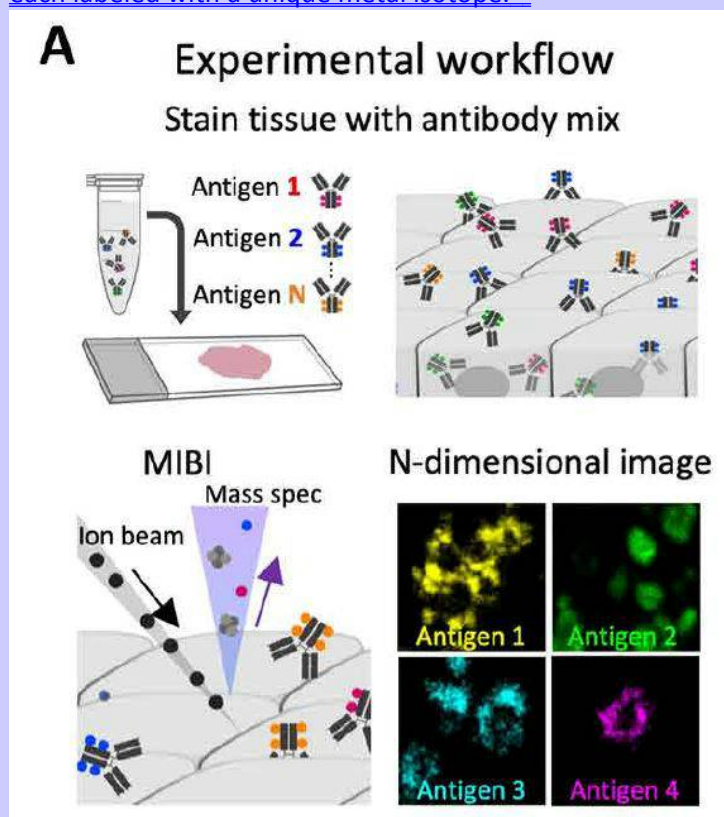
Comprehensive Capture of Human Neuropathology by Multiplexed Ion Beam Imaging (MIBI)

Webinar presented by Sean Bendall, MD. Ph.D, Principal Investigator, The Stanford Blood Center

Abstract: Single cell analysis, starting with the earliest low parameter fluorescent experiments, helped define the major cell subsets of human cellular systems as we understand them today. Now, a novel combination of single cell analysis and metal isotopes based mass spectrometry (MIBI) offers a routine examination of 30+ parameters at the nanometer scale, without interference of spectral overlap characteristic of fluorescent reporters. With this platform, we have reached new levels of organizational understanding in human pathobiology – especially when combined with novel single-cell visualization and analysis methods.

<https://www.ionpath.com/webinars/>

In the 2019 article by Keren, et al., the MIBI experimental procedure begins with “a tissue section [that] is stained with a mix of antibodies, each labeled with a unique metal isotope.”



Source: <https://advances.sciencemag.org/content/5/10/eaax5851>

146. ~~106.~~ At all relevant times, on information and belief, IONpath's acts of infringement of the '386 Patent have been committed and are being committed willfully, post-suit, with full knowledge and notice of Fluidigm's rights in and to the '386 Patent including, but not limited to, the claims set forth therein.

147. ~~107.~~ As a direct and proximate result of IONpath's infringement of the '386 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm's lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

148. ~~108.~~ As a direct and proximate result of IONpath's acts of infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath's infringing acts are enjoined and restrained by order of this Court.

COUNT III
INDIRECT PATENT INFRINGEMENT
(The '386 Patent)

149. ~~109.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

150. ~~110.~~ IONpath has induced and continues to induce infringement of one or more claims of the '386 Patent under 35 U.S.C. § 271(b).

151. ~~111.~~ As discussed above, IONpath commercialized a ~~"purpose-built" MIBIscope that requires~~ product specifically designed, manufactured, produced, and built with the intent that it only be employed by users to implement "a method that uses secondary ion mass spectrometry

to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” combined with “time-of-flight mass spectrometry;” for "single cell analysis and metal isotopes mass spectrometry." which results in any entity using the MIBIScope-~~users~~ infringing upon at least exemplary claim 9 of the ‘386 Patent. In other words, the MIBIScope was and is “purpose-built” to directly perform the steps required by at least exemplary claim 9 of the ‘386 Patent.

152. IONpath indisputably gained full notice and knowledge of the ‘386 Patent and IONpath’s infringement of one or more claims of the ‘386 Patent when it was served with the Original Complaint in this lawsuit on September 23, 2019.

153. After Fluidigm served the Original Complaint alleging IONpath infringed Fluidigm’s ‘386 Patent and including a claim chart detailing IONpath’s exemplary infringing activity, IONpath intentionally announced the formal commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the **MIBIScope™ System**, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

See <https://www.ionpath.com/news/>.

154. By announcing its formal commercial launch of its infringing MIBIScope after its knowledge of its infringement, IONpath intended to, and did, sell the MIBIScope to third-parties, even though IONpath knew that MIBIScope’s only purpose and function results in the

infringement of one or more claims of the '386 Patent including, but not limited to, exemplary claim 9.

155. IONpath also hosted a booth, and through its founder Dr. Angelo presented, at the 2019 SITC Meeting recommending and teaching attendees of the conference on using the MIBIScope for its designed, and sole, purpose, which infringes on claims of the '386 Patent including, but not limited to, exemplary claim 9. IONpath's co-presenters also detailed how IONpath representatives offered technical support to assist to teach the co-presenters' institutions in using the MIBIScope to infringe on claims of the '386 Patent including, but not limited to, exemplary claim 9.

156. IONpath also intentionally had its founders publish the 2020 Article and 2020 Review advertising, encouraging, and instructing third-parties on how to perform and infringe the method set forth in the '386 Patent including, but not limited to, exemplary claim 9. In the 2020 Article, for example, IONpath taught third-parties how to infringe on at least exemplary claim 9 of the '386 Patent by explaining in detail to third-parties the "use of heavy metal-conjugated antibodies that are quantified by TOF MS, thus allowing highly multiplexed, single-cell and imaging assays," using the MIBIScope. In the 2020 Review, for example, IONpath explained that its MIBI System was developed for the sole purpose of analyzing samples stained with antibodies tagged with metal-isotopes through a method wherein the sample has secondary ions released through the use of an ion beam raster scanned across the sample, wherein the secondary ions are then passed through the detection system to complete the process, which infringes on claims of the '386 Patent including, but not limited to, exemplary claim 9.

157. ~~112.~~ IONpath also offers for sale the MIBItag reagents which provide isotopically labelled antibodies for use with the MIBIScope, and/or has encouraged the use of Fluidigm's proprietary Maxpar[®] Reagents with the MIBIScope. IONpath has published results obtained with the MIBIScope and identifying both the Maxpar[®] Reagents and MIBItags as the labeling reagents (in the 2018 Article referred to above, *see* Supplementary Material, page e1, Critical Commercial Assays).

STAR★METHODS

KEY RESOURCES TABLE

| | | |
|---|---------------------|----------------|
| Critical Commercial Assays | | |
| Maxpar X8 Antibody labeling kit | Fluidigm | Cat#2011XXX |
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| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

158. ~~113.~~ In addition to directly infringing at least one claim of the '386 Patent including, but not limited to, exemplary claim ~~1~~,9, IONpath indirectly and intentionally infringes at least exemplary claim ~~19~~ of the '386 Patent by among other things, instructing, directing, and/or requiring others, including customers, purchasers, users, and developers, through IONpath's commercial launch of the MIBIScope, presentations at the 2019 SITC Meeting, 2020 Article, and 2020 Review to perform the method claimed in at least exemplary claim ~~1~~,9, either literally and/or under the doctrine of equivalents, through the sale of the MIBIScope, and MIBItags, where the claimed methods are performed by either IONpath or its customers, purchasers, users, and developers, or some combination thereof. As of the September 23, 2019, when Fluidigm served IONpath with the Original Complaint, IONpath knew and/or was willfully blind to the fact that it was inducing others, including customers, purchasers, users, and

developers, to infringe one or more claims of the '386 Patent by practicing, either themselves or in conjunction with ~~the~~ IONpath, one or more method claims of the '386 Patent, through sales of the MIBIScope.

159 ~~114.~~ Post-suit (i.e., after receiving notice of this lawsuit), IONpath has knowingly and actively aided and abetted the direct infringement of the '386 Patent by instructing and encouraging its customers, purchasers, users, and developers by commencing IONpath's commercial launch of the MIBIScope, presentations at the 2019 SITC Meeting, 2020 Article, and 2020 Review to use its MIBIScope product and its MIBItag isotopically labelled antibodies. Such instructions and encouragement ~~included~~ include, but are not limited to, advising third parties to use the MIBIScope, as IONpath's customers presented on at the 2019 SITC Meeting, and MIBItag isotopically labelled antibodies, in an infringing manner, providing a mechanism through which third parties may infringe the '386 Patent, advertising and promoting the use of MIBIScope product and MIBItags in an infringing manner, and distributing guidelines and instructions to third parties on how to use MIBIScope and MIBItags in an infringing manner. ~~For example, IONpath's 2018 brochure "MIBIScope™ I: Multiplexed Tissue Imaging that Transforms Discovery" advertises the benefits and advantages of the MIBIScope for performing mass cytometry methods, and describes how it may be used. IONpath's 2019 "MIBI™ Reagents for High Multiplex Tissue Imaging (Get Results You Can Trust)" advertises the benefits and advantages of IONpath's isotopically conjugated antibodies (MIBItags), and described how they can be used for mass cytometry methods. IONpath's website also provides general instructions~~

~~and explanations for the use of the MIBIScope and MIBItags, along with contact information for obtaining further information and/or ordering these products.~~

160. For example, IONpath's official commercial launch of the MIBIScope on November 5, 2019, after it was served with the Complaint in this action, promoted the purchase of the MIBIScope to image biomarkers within a sample through the use of staining a sample, removing a layer of the sample by directing an ion beam at a section of tissue with sufficient energy to liberate and generate secondary ions constituting "vaporizing, atomizing and ionizing" the metal labelled antibodies in a manner that infringes the claims of the '386 Patent. IONpath's CEO, Harris Fienberg, promoted, recommended, and encouraged using the MIBIScope to infringe on the '386 Patent to gain "unprecedented insights into spatial relationships with the tissue microenvironment by imaging and characterizing tissue samples at subcellular resolution." IONpath's CEO further admitted that prior to bringing the MIBIScope to market, IONpath piloted it with research and biopharma institutions instructing those institutions on how to use the MIBIScope by employing methods that infringe upon the '386 Patent.

161. By directing an ion beam at a section of tissue with sufficient energy to generate secondary ions, IONpath's MIBIScope is "vaporizing, atomizing and ionizing" the elemental tags of the lanthanide labeled antibodies in a manner that infringes the claims of the '386 Patent either literally and/or under the doctrine of equivalents. The 2019 Cell article to Keren describes and shows the creation of secondary ions from the elemental tags by directing the ion beam onto the tissue sample. In so doing, the MIBIScope is directing ions at sufficiently high energies at the sample, such that the impact of the ions on the sample transfers energy to the sample, and this

transfer of energy causes the elemental tags to become excited and liberated from the chemical moieties to which they are attached. The resulting excited and liberated elemental tags (i.e., the ionized lanthanide tags) are no longer in a solid or lattice matrix or in a solution and have been vaporized. The ionized metal tags have been liberated as constituent ionized atoms and have been atomized. The ionized metal tags have also been excited and thus have been vaporized, atomized, and ionized for purposes of the claims of the '386 Patent. Further, the MIBIscope is "vaporizing, atomizing, and ionizing" the elemental tags under the doctrine of equivalents because the ion beam liberates and excites the elemental tags so that the ionized elemental tags can be detected by mass spectrometry. As a result, the primary ion beam generates liberated secondary ions from the elemental tags for detection and performs substantially the same function in substantially the same way to obtain the same result. Accordingly, by promoting the purchase and use of the MIBIscope, and by providing instructing on how to use the instrument, IONpath has induced infringement of the '386 Patent.

162. ~~115.~~ As a direct and proximate result of IONpath's post-suit indirect infringement of the '386 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm's lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

163. ~~116.~~ As a direct and proximate result of IONpath's post-suit acts of indirect infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath's infringing acts are enjoined and restrained by order of this Court.

COUNT IV
CONTRIBUTORY PATENT INFRINGEMENT
(The '386 Patent)

164. ~~117.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully recited and incorporated herein.

165. ~~118.~~ IONpath has contributed and continues to contribute to the infringement of one or more claims of the '386 Patent under 35 U.S.C. § 271(c).

166. ~~119.~~ IONpath commercialized a “purpose-built” MIBIScope that ~~implements~~is specially designed for, and only serves one purpose, which is implementing a method patented by Fluidigm “that uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” combined with “time-of-flight mass spectrometry.” When analyzing tissue cells with the MIBIScope combined with antibodies tagged with lanthanide or noble metal tags, the MIBIScope user infringes upon a method covered under one or more claims of the '386 Patent including, but not limited to, as set forth in, for example, exemplary claim ~~19~~ of the '386 Patent.

167. ~~120. On information and belief, beginning in 2018 or earlier, with an expected commercial launch date in 2019, After Fluidigm filed this lawsuit alleging IONpath's infringement of the '386 Patent, IONpath knowingly, intentionally, and willfully began marketing continued to market and selling sell the infringing MIBIScope machine, including, for example, the commercial launch on November 5, 2019, as well as presenting on, and selling, the MIBIScope at the 2019 SITC Meeting. The MIBIScope is a physical apparatus with a price tag at,~~

or in excess of, \$1,000,000.00 specially designed to solely implement Fluidigm's patented-method methods set forth in the Patents.

168. The only purpose served by the MIBIScope is that of using "mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections" combined with "time-of-flight mass spectrometry." The "antibodies tagged with isotopically pure elemental metal reporters" are the MIBItags (or Fluidigm's Maxpar reagents), which are specifically created for that purpose. The antibodies are selected and engineered for their specific affinity for particular biomarkers of interest within a sample or cell. The selected antibodies are covalently linked to a particular type of polymer containing multiple binding cites for selected lanthanide tags, which allows them to serve their sole purpose and the sole purpose of the MIBIScope, which infringes at least exemplary claim 9 of the '386 Patent. The MIBIScope and MIBItags have no other purpose.

169. ~~121. On information and belief~~Accordingly, the MIBIScope is a "purpose-built" machine that does not serve any non-infringing use, but is solely designed to practice the method of at least ~~Claim 1~~exemplary claim 9 of the '386 patent.

170. ~~122.~~ IONpath has commercialized MIBItags which are isotopically labelled antibodies that implement the method of at least ~~Claim 1~~exemplary claim 9 of the '386 patent. When analyzing tissue cells with the MIBItags combined with mass cytometry using the MIBIScope, the MIBItag user infringes upon a patented method as set forth in, for example, exemplary claim ~~1~~9 of the '386 Patent.

~~123.—On information and belief, beginning at least in 2019, IONpath began marketing and selling the infringing MIBItags. The MIBItags are isotopically labelled antibodies designed to implement Fluidigm’s patented method.—~~

~~171. 124. On information and belief, the~~The MIBItags are specifically designed for use in the infringing methods of the ‘386 Patent and do not serve any non-infringing use.

~~172. 125.~~As a direct and proximate result of IONpath’s post-suit contributory infringement of the ‘386 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm’s lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

~~173. 126.~~As a direct and proximate result of IONpath’s post-suit acts of contributory infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath’s infringing acts are enjoined and restrained by order of this Court.

COUNT V
DIRECT PATENT INFRINGEMENT
(The ‘104 Patent)

~~174. 127.~~Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully recited and incorporated herein.

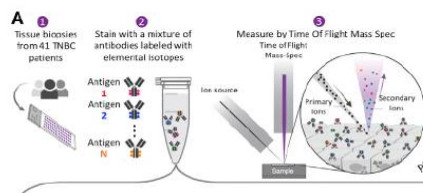
~~175. 128.~~On September 11, 2018, the U.S. Patent and Trademark Office duly and legally issued the ‘104 Patent.

~~176. 129.~~Fluidigm is the owner, by assignment and through its wholly owned subsidiary, of all right, title, and interest in and to the ‘104 Patent, including, but not limited to, the right to recover damages for past and future infringement.

177. ~~130.~~ IONpath has been and is directly infringing, literally and/or under the doctrine of equivalents, the '104 Patent in violation of 35 U.S.C. § 271 by, among other things, using systems and methods for the analysis of a single cell including, but not limited to, staining by a mixture of antibodies tagged with elemental tags of lanthanide or noble metal, ionizing, and then analyzing using mass spectroscopy and time of flight analysis to detect the signal of the ionized elemental tags, which methods are covered by one or more of the claims of the '104 Patent, including, but not limited to, exemplary claim ~~1.~~14.

178. ~~131.~~ On information and belief, at least with respect to the subject matter of the methods described and claimed in the '104 Patent, the use of the MIBIScope for performing mass spectrometry analysis directly infringes at least exemplary claim ~~1.~~14 of the '104 Patent.

179. ~~132.~~ As IONpath states in its 2018 Article, IONpath's apparatus infringes on Fluidigm's '104 Patent, ~~Claim 1,~~exemplary claim 14, by implementing a method wherein IONpath analyzes "specimens . . . placed on a slide and stained overnight using a single mater mix of elementally labeled primary antibodies." The slide is then "placed in the MIBI-TOF mass spectrometer" for analysis. IONpath's description of the method used by its apparatus also confirms that the analysis does not require prior acidification of the sample. This is summarized in Figure 1A of the 2018 Article:



180. IONpath announced the commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the **MIBIScope™ System**, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

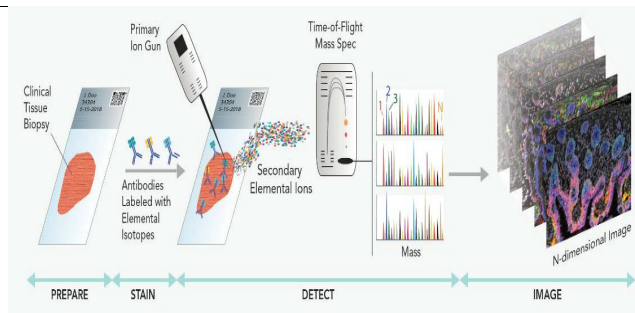
See <https://www.ionpath.com/news/>

181. ~~133.~~ IONpath has also used and commercialized MIBItags that are isotopically labelled antibodies that implement Fluidigm's patented method when combined with IONPath's MIBIScope.

182. ~~134.~~ A chart setting out the elements of exemplary claim 14 of the '104 Patent; (and ~~the~~ including the elements of claim 1, from which claim 14 depends), and certain, but not all, representative corresponding infringing activities of IONpath, is below.

'104 Patent

| Claim Limitation | IONpath/customer activities |
|---|--|
| 1. A method for the analysis of an analyte in a sample, comprising: | <p>IONpath's MIBIScope <u>IONpath's MIBI technology system (the "MIBI System"), which include the MIBIScope in combination with IONpath's MIBItag reagents or other suitable reagent (e.g. Fluidigm's Maxpar reagents), performs a method for the analysis of an analyte in a sample.</u></p> <p><u>IONpath's MIBIScope system provides, for example, for imaging of antibodies within a biological sample.</u></p> <p><u>https://www.ionpath.com/mibi-technology/</u></p> |



<https://www.ionpath.com/>

High Multiplex Capability

Simultaneously stain and detect 40+ targets and observe cells with the whole picture of an intact tissue tumor microenvironment.

<https://web.stanford.edu/group/nolan/technologies.html>

Multiplexed ion beam imaging (MIBI) allows analyzing up to 100 targets simultaneously over a five-log dynamic range in **a way similar to CyTOF**, but in addition to **measuring protein levels on individual cells**, it also provides the information about cell morphology and localization.

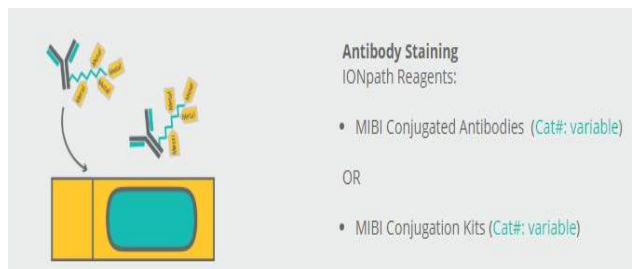
(i) incubating an element tagged affinity reagent with an analyte, the element tagged affinity reagent comprising an affinity reagent tagged with an element tag,

IONpath's ~~MIBItags~~ are used for incubating MIBI System includes the MIBIScope that uses MIBItags (or Fluidigm's Maxpar reagents) as an element tagged affinity reagent for incubating with an analyte, the element tagged affinity reagent comprising an affinity reagent tagged with an element tag, the element tag comprising a linear or branched polymer having multiple metal-binding pendant groups, wherein each pendant group includes at least one metal atom or is capable of binding at least one metal atom, and wherein the affinity reagent specifically binds with the analyte, wherein the analyte is located within or on an intact cell.

<https://www.ionpath.com/mibi-technology/>

STAIN: Tissue is stained with a mixture of validated **antibodies** with conjugated **elemental reporters**, in one single step.

<https://www.ionpath.com/reagents/>



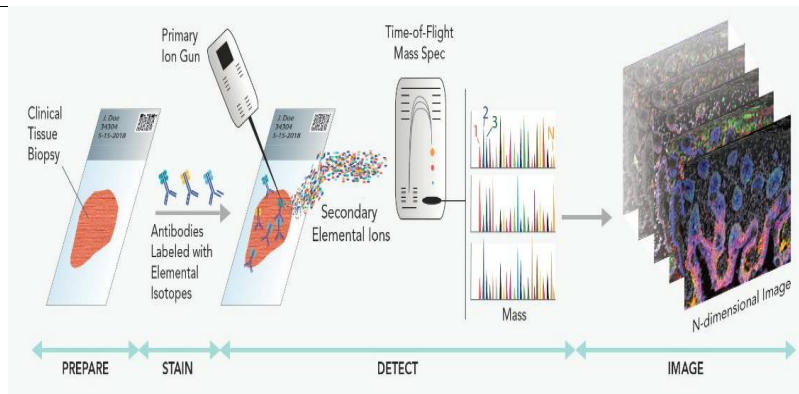
The Safety Data sheets for the **MIBItag** conjugation kits disclose, for example, that the MIBItags are comprised of a metal elemental tag and a polymer. For example, the SDS pictured before for MIBItag Conjugations Kit (Y), which lists a lanthanide as its elemental tag, and a polymer component containing DTPA.

| | |
|---------------------------|--|
| Product identifier | MIBItag Conjugation Kit (Y) |
| Synonyms | None identified |
| Trade names | None identified |
| Chemical family | Lanthanide component Mixture - contains nitric acid and m Stabilization Buffer component Mixture – contains sodium a Polymer component – contains diethylenetriaminepentaaceti |

Source:

http://ionpath.wpengine.com/wp-content/uploads/2018/09/SDS_IONLabel_Y_V1b.pdf

[IONpath's MIBItags binds with specific analytes within or on a cell.](#)



Source: <https://www.ionpath.com/mibi-technology/>

the element tag comprising a linear or branched polymer having multiple metal-binding pendant groups, wherein each pendant group includes at least one metal atom or is capable of binding at least one metal atom,

IONpath's MIBI System uses MIBItags ~~are used~~ (or Fluidigm's Maxpar reagents) for providing the element tag comprising a linear or branched polymer having multiple metal-binding pendant groups, wherein each pendant group includes at least one metal atom or is capable of binding at least one metal atom

SDS from <https://www.ionpath.com/antibody-conjugation-kit/>

| | |
|--------------------|---|
| Product identifier | MIBItag Conjugation Kit (Y) |
| Synonyms | None identified |
| Trade names | None identified |
| Chemical family | Lanthanide component Mixture - contains nitric acid and metal lanthanide Stabilization Buffer component Mixture - contains sodium azide Polymer component - contains diethylenetriaminepentaacetic acid |

2018 Cell Publication

<https://doi.org/10.1016/j.cell.2018.08.039>


STAR★METHODS

KEY RESOURCES TABLE

| | | |
|---|---------------------|----------------|
| Critical Commercial Assays | | |
| Maxpar X8 Antibody labelling kit | Fluidigm | Cat#2011XXX |
| MIBItag Conjugation Kit | IONpath | Cat#600XXX |
| ImmPRESS UNIVERSAL (Anti-Mouse/Anti-Rabbit) IgG KIT (HRP) | Vector Laboratories | Cat#MP-7500-15 |
| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

and wherein the affinity reagent specifically binds with the analyte, wherein

IONpath's MIBI System uses MIBItags ~~are used~~ (or Fluidigm's Maxpar reagents) to provide an affinity reagent that specifically binds with the

| | |
|---|--|
| the analyte is located within or on an intact cell; | <p>analyte, wherein the analyte is located within or on an intact cell</p> <p>https://www.ionpath.com/</p> <p>FFPE Tissue Staining</p> <p>Follow a classic multiplexed IHC protocol using IONpath pathologist-validated or custom antibodies with any FFPE samples.</p> <p>High Multiplex Capability</p> <p>Simultaneously stain and detect 40+ targets and observe cells with the whole picture of an intact tissue tumor microenvironment.</p> |
| (ii) separating unbound element tagged affinity reagent from bound element tagged affinity reagent; and | <p>IONpath's use of IONpath's MIBI System including the MIBIscope and MIBItags involves <u>(or as combined with Fluidigm's Maxpar reagents) perform</u> separating unbound element -tagged affinity reagent from bound -element -tagged affinity reagent.</p> <p>https://www.ionpath.com/slides-and-reagents/</p> <p>IONpath's MIBI 20x TBS-T reagent is "use as a wash buffer to remove nonspecific antibody binding and as a blocking buffer diluent in the MIBI Staining Protocol."</p> <p></p> <p>Technical Data Sheet</p> <p>MIBI 20X TBS-T</p> <p>Catalog: 567005 Storage: Store at 4°C</p> <p>Description: Tris buffered saline (TBS), pH 7.6, with the detergent Tween® 20 is intended to be used as a wash buffer to remove nonspecific antibody binding and as a blocking buffer diluent in the MIBI Staining Protocol.</p> <p>Source: https://www.ionpath.com/wp-content/uploads/2018/09/20X-TBS-T-567005-TDS.pdf</p> |
| (iii) analyzing the element tag bound to the affinity reagent attached to the analyte of the intact cell by atomic spectroscopy, wherein analyzing occurs | <p>IONpath's MIBI System <u>uses a MIBIscope that</u> performs steps of analyzing <u>of</u> the element -tag <u>which is</u> bound to the affinity reagent attached to the analyte of the intact cell by atomic spectroscopy, wherein analyzing occurs without prior acidification of the sample <u>cell</u>.</p> |

without prior acidification of the sample.

MIBIscope's "subcellular resolution" provides "[c]ellular structures as small as 250 nm [to] be imaged."

True Sub-Cellular Resolution

With resolution comparable to light microscopy systems, MIBIscope system lets you analyze and interpret cellular interactions. Cells as small as 250 nm can be imaged, enabling downstream cell segmentation data analysis. Because the MIBIscope doesn't fully ablate the sample, it can be done to select specific regions of interest followed by high-resolution imaging.

Source: <https://www.ionpath.com/mibi-technology/>

<https://www.ionpath.com/>

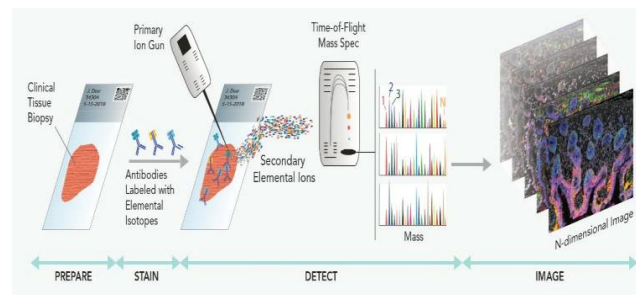
High Multiplex Capability

Simultaneously stain and detect 40+ targets and observe cells with the whole picture of an intact tissue tumor microenvironment.

<https://www.ionpath.com/mibi-technology/>

MIBI™ technology (Multiplexed Ion Beam Imaging) uses Secondary-Ion Mass Spectrometry (SIMS), a type of mass spectrometry traditionally used in the semiconductor industry, to image antibodies tagged with monoisotopic metal reporters.

IMAGE: All markers are imaged at the same time and detected via TOF mass spectrometry.



14. The method of claim 1, wherein the affinity reagent is an antibody.

IONpath's MIBI System includes the MIBIscope that uses MIBItags (or Fluidigm's Maxpar reagents), to provide an affinity reagent that is an antibody.

"Antibody conjugation kits provide the flexibility to label your antibody of interest with the metal you desire."



183. ~~135.~~ At all relevant times, on information and belief, IONpath's acts of infringement of the '104 Patent have been committed and are being committed with full knowledge of Fluidigm's rights in the '104 Patent.

184. ~~136.~~ As a direct and proximate result of IONpath's infringement of the '104 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm's lost profits, but no less than a reasonable royalty, in an amount to be determined at trial.

185. ~~137.~~ As a direct and proximate result of IONpath's acts of infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath's infringing acts are enjoined and restrained by order of this Court.

COUNT VI
INDIRECT PATENT INFRINGEMENT
(The '104 Patent)

186. ~~138.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

187. ~~139.~~ IONpath has induced and continues to induce infringement of one or more claims of the '104 Patent under 35 U.S.C. § 271(b).

188. As discussed above, IONpath commercialized a product specifically designed, manufactured, produced, and built with the intent that it only be employed by users to implement “a method that uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” combined with “time-of-flight mass spectrometry,” which results in any entity using the MIBIScope infringing upon at least exemplary claim 14 of the '104 Patent. In other words, the MIBIScope was and is “purpose-built” to directly perform the steps required by at least exemplary claim 14 of the '386 Patent.

189. IONpath had notice of the '104 Patent in September 2018, but indisputably also gained full knowledge of IONpath's infringement of one or more claims of the '104 Patent when it was served with the Original Complaint in this lawsuit on September 23, 2019.

190. After Fluidigm served IONpath with the Original Complaint alleging IONpath infringed Fluidigm's '104 Patent and including a claim chart detailing IONpath's exemplary infringing activity, IONpath intentionally announced the formal commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the MIBIScope™ System, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

[See https://www.ionpath.com/news/](https://www.ionpath.com/news/)

191. By announcing its formal commercial launch of its infringing MIBIScope after its knowledge of its infringement, IONpath intended to, and did, sell the MIBIScope to third-parties, even though IONpath knew that MIBIScope's only purpose and function results in the infringement of one or more claims of the '104 Patent including, but not limited to, exemplary claim 14.

192. IONpath also hosted a booth, and through its founder Dr. Angelo presented, at the 2019 SITC Meeting recommending and teaching attendees of the conference on using the MIBIScope for its designed, and sole, purpose, which infringes on the '104 Patent including, but not limited to, exemplary claim 14. IONpath's co-presenters also detailed how IONpath representatives offered technical support to assist to the co-presenters institutions in using the MIBIScope to infringe on the '104 Patent including, but not limited to, exemplary claim 14.

193. IONpath also intentionally had its founders publish the 2020 Article and 2020 Review advertising, encouraging, and instructing third-parties on how to perform and infringe the method set forth in the '104 Patent including, but not limited to, exemplary claim 14. In the 2020 Article, for example, IONpath taught third-parties how to infringe on at least exemplary claim 14 of the '104 Patent by explaining in detail to third-parties the "[a]ntibodies were

conjugated to heavy-metal ions with MaxPar (Fluidigm) or MIBItag (IONpath) reagents using an optimized conjunction protocol.” In the 2020 Review, for example, IONpath explained that its MIBI System was developed for the sole purpose of analyzing samples stained with antibodies tagged with metal-isotopes, which infringes on claims of the ‘104 Patent including, but not limited to, exemplary claim 14.

194. ~~140.~~ In addition to directly infringing at least one claim of the ‘104 Patent, including, but not limited to, exemplary claim ~~1,14~~, IONpath indirectly and intentionally infringes at least exemplary claim ~~1,14~~ of the ‘104 Patent by among other things, instructing, directing, and/or requiring others, including customers, purchasers, users, and developers, through IONpath’s commercial launch of the MIBIScope, presentations at the 2019 SITC Meeting, 2020 Article, and 2020 Review to perform the method claimed in at least exemplary claim ~~1,14~~, either literally and/or under the doctrine of equivalents, through the sale of the MIBIScope ~~(IONpath’s MIBI-TOF apparatus)~~, and MIBItags, where the claimed methods are performed by either IONpath or its customers, purchasers, users, and developers, or some combination thereof. As of the September 23, 2019, when Fluidigm served IONpath with the Original Complaint, IONpath knew and/or was willfully blind to the fact that it was inducing others, including customers, purchasers, users, and developers, to infringe one or more claims of the ‘104 Patent by practicing, either themselves or in conjunction with ~~the~~ IONpath, one or more method claims of the ‘104 Patent, through sales of the MIBIScope. ~~141.— IONpath knowingly and actively aided and abetted the direct infringement of the ‘104 Patent by instructing and encouraging its customers, purchasers, users, and developers to use its MIBIScope product. Such~~

~~instructions and encouragement included, but are not limited to, advising third parties to use MIBIScope in an infringing manner, providing a mechanism through which third parties may infringe the ‘104 Patent, advertising and promoting the use of MIBIScope product in an infringing manner, and distributing guidelines and instructions to third parties on how to use MIBIScope in an infringing manner. For example, IONpath’s 2018 brochure “MIBIScope™ I: Multiplexed Tissue Imaging that Transforms Discovery” from advertises the benefits and advantages of the MIBIScope for performing mass cytometry methods, and describes how it may be used. IONpath’s website also provides general instructions and explanations for the use of the MIBIScope, along with contact information for further information on these products.~~

195. 142. Post-suit, IONpath also has knowingly and actively aided and abetted the direct infringement of the ‘104 Patent by instructing and encouraging its customers, purchasers, users, and developers ~~to use~~by commencing IONpath’s commercial launch of the MIBIScope, presentations at the 2019 SITC Meeting, 2020 Article, and 2020 Review to use its MIBIScope product and its MIBItag isotopically ~~conjugated~~labelled antibodies ~~with its MIBIScope product.~~ Such instructions and encouragement ~~included~~include, but are not limited to, advising third parties to use the ~~MIBItags~~MIBIScope, as IONpath’s customers presented on at the 2019 SITC Meeting, and MIBItag isotopically labelled antibodies, in an infringing manner, providing a mechanism through which third parties may infringe the ‘104 Patent, advertising and promoting the use of MIBIScope product and MIBItags in an infringing manner, and distributing guidelines and instructions to third parties on how to use MIBIScope and MIBItags in an infringing manner. ~~For example, IONPath’s 2019 “MIBI™ Reagents for High Multiplex Tissue Imaging (Get~~

~~Results You Can Trust)” advertises the benefits and advantages of IONpath’s isotopically conjugated antibodies (MIBItags), and described how they can be used for mass cytometry methods. IONpath’s website also provides general instructions and explanations for the use of the MIBItags, along with contact information for obtaining further information and/or ordering these products.~~

196. ~~143.~~ As a direct and proximate result of IONpath’s post-suit, indirect infringement of the ‘104 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm’s lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

197. ~~144.~~ As a direct and proximate result of IONpath’s post-suit acts of indirect infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath’s infringing acts are enjoined and restrained by order of this Court.

COUNT VII
CONTRIBUTORY PATENT INFRINGEMENT
(The ‘104 Patent)

198. ~~145.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully recited and incorporated herein.

199. ~~146.~~ IONpath has contributed and continues to contribute to the infringement of one or more claims of the ‘104 Patent under 35 U.S.C. § 271(c).

200. ~~147.~~ IONpath commercialized its MIBIScope (IONpath’s MIBI-TOF apparatus) that ~~implements~~ is specially designed for, and only serves one purpose, which is implementing a

method patented by Fluidigm by analyzing antibodies stained with multiple metal tags that will specifically bind with specified analytes located within or on intact cells, by means of spectroscopy without prior acidification of the sample. IONpath has also commercialized its MIBItag isotopically labelled antibodies for use with the patented method. When analyzing tissue cells with the MIBIScope that have been stained with multiple lanthanide or noble metal tags, the MIBIScope user infringes upon a method covered under one or more claims of the ‘104 Patent including, but not limited to, as set forth in, for example, exemplary claim ~~+14~~ of the ‘104 Patent. Similarly, when staining cells with the MIBItags and then analyzing tissue cells with the MIBIScope, the MIBItag user infringes upon a patented method as set forth in, for example, exemplary claim ~~+14~~ of the ‘104 Patent.

201. ~~148. On information and belief, beginning in 2018 or earlier, with an expected commercial launch date in 2019, After Fluidigm filed this lawsuit alleging IONpath’s infringement of the ’104 Patent, IONpath knowingly, intentionally, and willfully began marketing continued to market and selling sell the infringing MIBIScope machine, including, for example, the commercial launch on November 5, 2019, as well as presenting on, and selling, the MIBIScope at the 2019 SITC Meeting. The MIBIScope is a physical apparatus with a price tag at, or in excess of, \$1,000,000.00 specially designed to solely implement Fluidigm’s patented method. IONpath is currently advertising the MIBItags for purchase on its website methods set forth in the Patents.~~

202. The only purpose served by the MIBIScope is that of using “mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections”

combined with “time-of-flight mass spectrometry.” The “antibodies tagged with isotopically pure elemental metal reporters” are the MIBItags (or Fluidigm’s Maxpar reagents), which are specifically created for that purpose. The antibodies are selected and engineered for their specific affinity for particular biomarkers of interest within a sample or cell. The selected antibodies are covalently linked to a particular type of polymer containing multiple binding sites for selected lanthanide tags, which allows them to serve their sole purpose and the sole purpose of the MIBIscope, which infringes at least exemplary claim 14 of the ‘104 Patent.

203. ~~149. On information and belief~~ Accordingly, the MIBIscope is a “purpose-built” machine that does not serve any non-infringing use, but is solely designed to practice the method of at least exemplary claim ~~14~~ of the ‘104 ~~Patent~~ patent.

204. ~~150.~~ IONpath has commercialized the MIBItags which are isotopically labelled antibodies that implement the method of at least exemplary claim ~~14~~ of the ‘104 Patent.

205. The MIBItags are specifically designed for use in the infringing methods of the ‘104 Patent and do not serve any non-infringing use.

206. ~~151.~~ As a direct and proximate result of IONpath’s post-suit contributory infringement of the ‘104 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm’s lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

207. ~~152.~~ As a direct and proximate result of IONpath’s post-suit acts of contributory infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath’s infringing acts are enjoined and restrained by order of this Court.

COUNT VIII
DIRECT PATENT INFRINGEMENT
(The ‘698 Patent)

208. ~~153.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

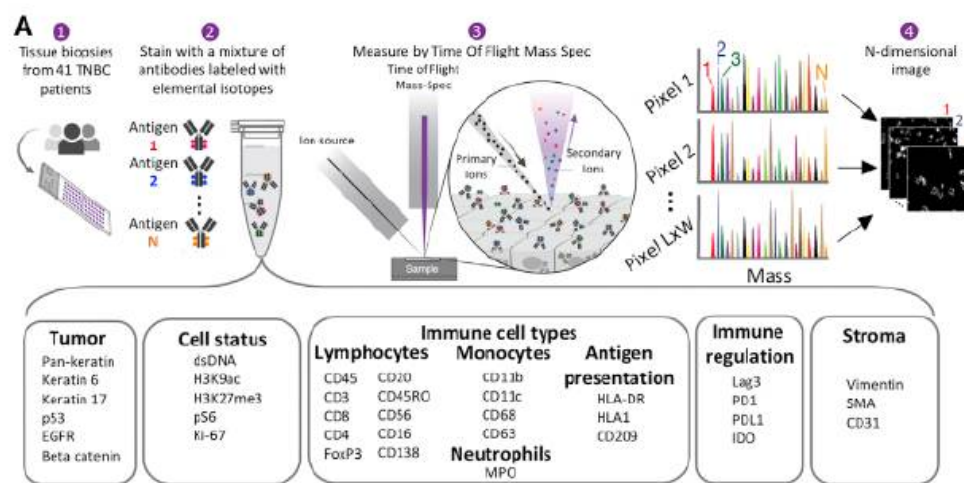
209. ~~154.~~ On October 8, 2019, the Patent Office duly and legally issued the ‘698 Patent.

210. ~~155.~~ Fluidigm is the owner, by assignment, of all right, title, and interest in and to the ‘698 Patent, including, but not limited to, the right to recover damages for past and future infringement.

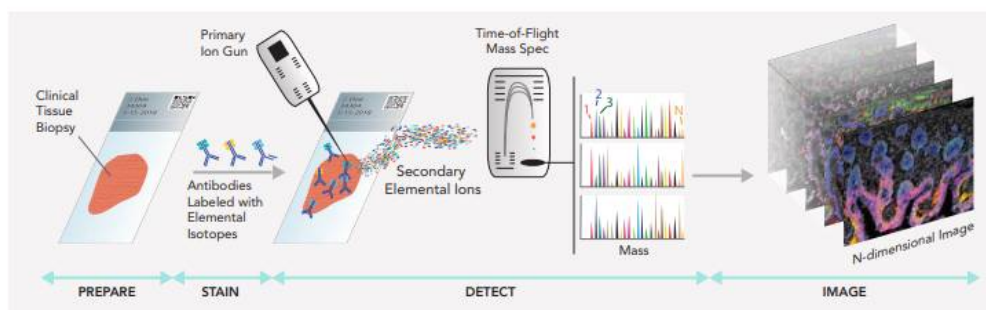
211. ~~156.~~ IONpath has been and is directly infringing, literally and/or under the doctrine of equivalents, the ‘698 Patent in violation of 35 U.S.C. § 271 by, among other things, making, using, offering for sale, and selling systems for the analysis of a single cell, including, but not limited to, systems devised to ionize and then analyze samples using mass spectroscopy and time of flight analysis to detect the signal of ionized elemental tags, where the samples are stained with a mixture of antibodies tagged with elemental tags of lanthanide or noble metal, which systems are covered by one or more of the claims of the ‘698 Patent, including, but not limited to, exemplary claim ~~1-6.~~

212. ~~157.~~ As IONpath published in the 2018 Article, IONpath constructed a “purpose-built instrument” that “uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” in combination

with “time-of-flight mass spectrometry” With respect to the operation of the instrument, the 2018 Article further describes that “tissue is subjected to a nanometer-scale, rasterizing oxygen duoplasma primary ion beam” and “[a]s this ion beam strikes the sample, elemental reporters conjugated to the antibodies are liberated as secondary ions, which are measured and quantified by a time-of-flight mass spectrometer.” This is further evidenced by, among other things, the system set forth in the summary IONpath included in the 2018 Article at Figure 1A:



213 ~~158~~ IONpath’s website also confirms in a brochure that its MIBIScope I contains the elements of Fluidigm’s patented system:



214. IONpath announced the commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the **MIBIScope™ System**, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

See <https://www.ionpath.com/news/>

215. ~~159.~~ IONpath has also commercialized MIBItags that are isotopically labelled antibodies that are designed for use with Fluidigm’s patented system. IONpath has used and advocated use of these MIBItags in combination with their infringing IONpath instruments on their website, and has published results obtained with the infringing MIBIScope and identifying MIBItags as the labeling reagents (in the 2018 Article referred to above, *see* Supplementary Material, page e1, Critical Commercial Assays).

STAR★METHODS

KEY RESOURCES TABLE


Critical Commercial Assays

| | | |
|---|---------------------|----------------|
| Maxpar X8 Antibody labeling kit | Fluidigm | Cat#2011XXX |
| MIBItag Conjugation Kit | IONpath | Cat#600XXX |
| ImmPRESS UNIVERSAL (Anti-Mouse/Anti-Rabbit) IgG KIT (HRP) | Vector Laboratories | Cat#MP-7500-15 |
| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

216. ~~160.~~ On information and belief, at least with respect to the subject matter of the systems disclosed and claimed in the ‘698 Patent, the making, using, offering for sale, and selling of the MIBIScope for performing mass spectrometry analysis directly infringes at least exemplary claim ~~16~~ of the ‘698 Patent.

217. ~~161.~~ A chart setting out the elements of exemplary claim ~~46~~ of the '698 Patent (and including the elements of claim 1, from which claim 6 depends), and certain, but not all, representative corresponding infringing activities of IONpath, is below.

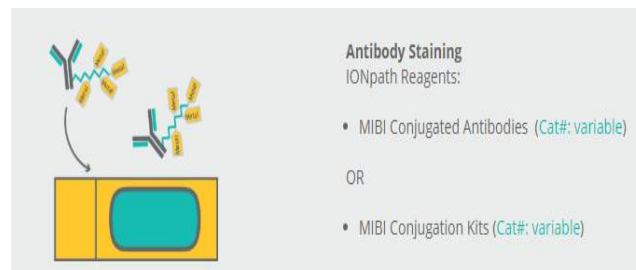
'698 Patent

| Claim Element | IONpath Activities |
|---|---|
| 1. A system for sequentially analyzing single cells in a sample by mass spectrometry, | <p>IONpath's MIBIscope MIBI technology system (the "MIBI System"), <u>which include the MIBIscope in combination with IONpath's MIBItag reagents or other suitable reagent (e.g. Fluidigm's Maxpar reagents),</u> is a system for sequentially analyzing single cells in a sample by mass spectrometry.</p> <p><u>The MIBI System images and analyzes individual or single cells using mass spectrometry as described by IONpath: "MIBI technology (Multiplexed Ion Beam Imaging) uses Secondary-Ion Mass Spectrometry (SMS)[.]"</u></p>  <p><u>Source: https://www.ionpath.com/mibi-technology/</u></p> <p><u>https://web.stanford.edu/group/nolan/technologies.html</u></p> <p><u>"Multiplexed ion beam imaging <u>imaging</u> (MIBI) allows analyzing up to 100 targets simultaneously over a five-log dynamic range in a way similar to CyTOF, but in addition to measuring protein levels on individual cells, it also provides the information about cell morphology and localization."</u></p> |

| | |
|--|---|
| | <p>Source: https://web.stanford.edu/group/nolan/technologies.html</p> <p><u>The MIBI System raster scans across a tissue sample with an ion beam, and thus scanning across the tissue from cell to cell sequentially:</u></p> <p><u>“Stationary tissue samples are raster-scanned with an ion beam and secondary elemental ions are generated.”</u></p> <p>Source: https://www.ionpath.com/mibi-technology/</p> |
| <p>wherein the sample comprises a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the plurality of tagged antibodies is specific for a different analyte, and wherein each of the plurality of tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal;</p> | <p>IONPath’s MIBI System uses MIBItags (or Fluidigm’s Maxpar reagents) which are used to create a sample comprising a plurality of tagged cells tagged with a plurality of tagged antibodies, wherein each of the plurality of tagged antibodies is specific for a different analyte, and wherein each of the plurality of tagged antibodies is tagged with an elemental tag comprising a lanthanide or noble metal</p> <p>https://www.ionpath.com/mibi-technology/</p> <p>STAIN: Tissue is stained with a mixture of validated antibodies with conjugated elemental reporters, in one single step.</p> <p>This unique technology enables:</p> <ul style="list-style-type: none"> • Visualization of 40+ markers simultaneously • Imaging at the sub-cellular resolution <p>2018 P106 Poster</p> <p>Samples were stained with a panel of 15 antibodies, each labeled with a specific metal isotope.</p> <p>https://www.ionpath.com/wp-content/uploads/2018/11/P106_ION</p> |

[poth_Ptacek_SITC-2018-2.pdf](#))

<https://www.ionpath.com/reagents/>



SDS from <https://www.ionpath.com/antibody-conjugation-kit/>

| | |
|--------------------|---|
| Product identifier | MIBitag Conjugation Kit (Y) |
| Synonyms | None identified |
| Trade names | None identified |
| Chemical family | Lanthanide component Mixture - contains nitric acid and metal lanthanide Stabilization Buffer component Mixture – contains sodium azide Polymer component – contains diethylenetriaminepentaacetic acid |

2018 Cell Publication

<https://doi.org/10.1016/j.cell.2018.08.039>

STAR★METHODS

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| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

wherein the system comprises:

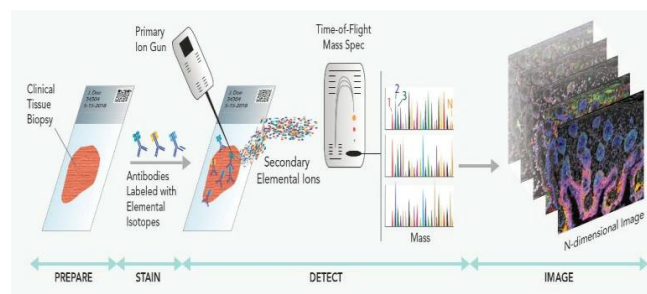
a first device to vaporize, atomize, and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a

IONpath's **MIBIscope** is a system having a first device to vaporize, atomize, and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a single second cell of the plurality of tagged cells

[IONpath's MIBIscope uses, for example, a primary ion gun to vaporize, atomize, and ionize each of a plurality of tagged cells.](#)

single second cell of the plurality of tagged cells;

<https://www.ionpath.com/mibi-technology/>



See also 2014 article with Nolan et al. on MIBI technique:

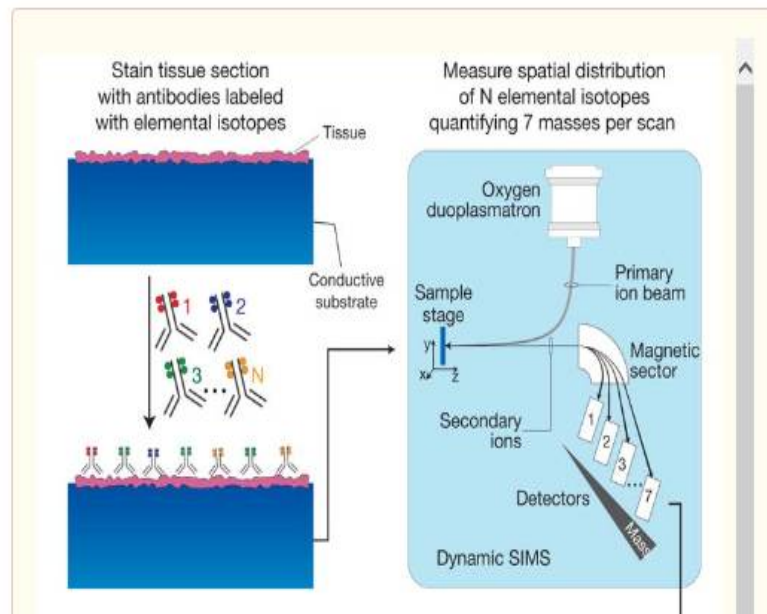
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110905/>), which describes that “[t]he specimens prepared for MIBI are mounted in a sample holder and subjected to a rasterized oxygen duoplasmatron primary ion beam. As this ion beam strikes the sample[,] lanthanide adducts of the bound antibodies are liberated as secondary ions.”

Results

Go to: 

Performance assessment of MIBI

The workflow for MIBI is comparable to IF and IHC assays (Fig. 1). Instead of fluorophores or enzyme-conjugated reagents, biological specimens are incubated with primary antibodies coupled to stable lanthanides highly enriched for a single isotope (Fig. 1). Primary antibodies are combined in solution for simultaneous incubation with the specimen. The specimens prepared for MIBI are mounted in a sample holder and subjected to a rasterized oxygen duoplasmatron primary ion beam. As this ion beam strikes the sample lanthanide adducts of the bound antibodies are liberated as secondary ions. In this study, the secondary ions are subsequently analyzed via a magnetic sector mass spectrometer equipped with multiple detectors, permitting parallel detection of multiple lanthanide isotopes (mass-based reporters). The resultant data produces a two-dimensional map of the elemental distribution of each lanthanide, and thus each antibody and its corresponding epitope.



a second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the

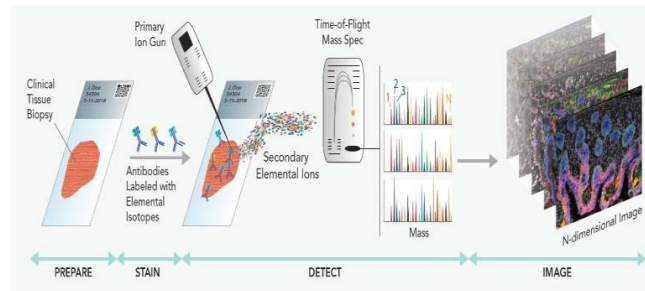
IONpath's **MIBIscope** is a system having a second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single first cell, and lanthanides and/or noble metals of the single second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single second cell, wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially

single first cell, and lanthanides and/or noble metals of the single second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single second cell, wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially.

<https://www.ionpath.com/mibi-technology/>

This unique technology enables:

- Visualization of 40+ markers simultaneously
- Imaging at the sub-cellular resolution



2018 Cell Publication

<https://doi.org/10.1016/j.cell.2018.08.039>

We have since constructed a purpose-built instrument that utilizes high brightness primary ion sources, novel ion extraction optics, and **time-of-flight mass spectrometry (TOF)** to increase channel multiplexing and decrease acquisition times 50-fold

6. The system of claim 1, wherein each of the plurality of tagged antibodies is tagged with a distinct isotope.

IONpath's MIBI System uses MIBItags (or Fluidigm's Maxpar reagents) to provide each of the plurality of tagged antibodies is tagged with a distinct isotope.

IONpath's MIBItag conjugation kits allow users, for example, to choose an isotope for each respective antibody, while the conjugated antibodies are sold pre-tagged.

Conjugation Kits

Antibody conjugation kits provide the flexibility to label your antibody of interest with the metal you desire.

- Each kit provides 4 antibody conjugation reactions for labeling 100 ug of antibody

Source: <https://www.ionpath.com/antibody-conjugation-kit/>

Conjugated Antibodies

IONpath offers IHC validated antibodies to obtain optimal performance and save you time and money in extensive validation.

- Each lot of conjugated antibody is quality control tested by MIBI analysis of stained tissue microarray

Source: <https://www.ionpath.com/conjugated-antibodies/>

MIBI Technology allows users “to image antibodies tagged with monoisotopic metal reporters” with “[v]isualization of 40+ markers

MIBI™ Technology

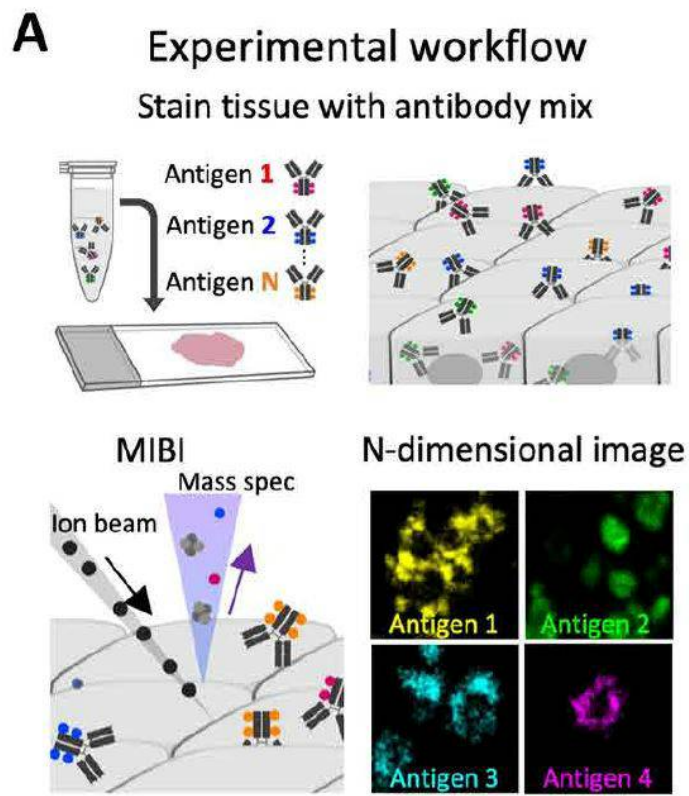
MIBI™ technology (Multiplexed Ion Beam Imaging) uses Secondary-Ion Mass Spectrometry (SIMS), a type of mass spectrometry traditionally used in the semiconductor industry, to image antibodies tagged with monoisotopic metal reporters. This unique technology enables:

- Visualization of 40+ markers simultaneously
- Imaging at the sub-cellular resolution
- Detection of low abundance proteins
- Rescanning of slides at multiple resolutions

simultaneously[.]”

Source: <https://www.ionpath.com/mibi-technology/>

In the 2019 article by Keren, et al., the MIBI experimental procedure begins with “a tissue section [that] is stained with a mix of antibodies, each labeled with a unique metal isotope.”



Source: <https://advances.sciencemag.org/content/5/10/eaax5851>

In IONpath webinars, the MIBIscope provides “single cell analysis and metal isotopes mass spectrometry.”

Comprehensive Capture of Human Neuropathology by Multiplexed Ion Beam Imaging (MIBI)

Webinar presented by Sean Bendall, MD, Ph.D, Principal Investigator, The Stanford Blood Center

Abstract: Single cell analysis, starting with the earliest low parameter fluorescent experiments, helped define the major cell subsets of human cellular systems as we understand them today. Now, a novel combination of single cell analysis and metal isotopes based mass spectrometry (MIBI) offers a routine examination of 30+ parameters at the nanometer scale, without interference of spectral overlap characteristic of fluorescent reporters. With this platform, we have reached new levels of organizational understanding in human pathobiology – especially when combined with novel single-cell visualization and analysis methods.

<https://www.ionpath.com/webinars/>

218. ~~162.~~ At all relevant times, on information and belief, IONpath's acts of infringement of the '698 Patent have been committed and are being committed willfully with full knowledge and notice of Fluidigm's rights in and to the '698 Patent, and its family, including, but not limited to, the claims set forth in the '698 Patent.

219. ~~163.~~ As a direct and proximate result of IONpath's infringement of the '698 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm's lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

220. ~~164.~~ As a direct and proximate result of IONpath's acts of infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath's infringing acts are enjoined and restrained by order of this Court.

COUNT IX
INDIRECT PATENT INFRINGEMENT
(The '698 Patent)

221. ~~165.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully restated and incorporated herein.

222. ~~166.~~ IONpath has induced and continues to induce infringement of one or more claims of the '698 Patent under 35 U.S.C. § 271(b).

223. ~~167.~~ As discussed above, IONpath commercialized ~~its MIBIScope instrument that "uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections" combined with "time-of-flight mass~~

~~spectrometry,” the operation of which results in the MIBIScope users infringing upon at least claim 1 of the ‘698 Patent.~~ a product specifically designed, manufactured, produced, and built for “secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” and “time-of-flight mass spectrometry” for “single cell analysis and metal isotopes mass spectrometry,” which results in any entity using the MIBIScope infringing upon at least claim 6 of the ‘698 Patent. In other words, the MIBIScope was and is “purpose-built” to directly meet the requirements of at least claim 6 of the ‘698 Patent.

224. IONpath indisputably gained full notice and knowledge of the ‘698 Patent and IONpath’s infringement of one or more claims of the ‘698 Patent when it was served with the First Amended Complaint in this lawsuit on October 11, 2019.

225. After Fluidigm served its First Amended Complaint in this lawsuit alleging IONpath infringed Fluidigm’s ‘698 Patent and including a claim chart detailing IONpath’s exemplary infringing activity, IONpath intentionally announced the commercial launch of its infringing MIBIScope instrument on November 5, 2019:

IONpath Announces Commercial Launch of MIBIScope™—the First Multiplexed Ion Beam Imaging System

MIBIScope allows researchers to visualize over 40 biomarkers simultaneously with high resolution, sensitivity, and throughput, and is compatible with standard tissue processing techniques

Menlo Park, Calif., November 5, 2019 – IONpath, Inc., a company revolutionizing multiplexed tissue imaging, launched the MIBIScope™ System, the first commercially available Multiplexed Ion Beam Imaging (MIBI™) system. The MIBIScope enables researchers to image over 40 biomarkers simultaneously at higher sensitivity, resolution, and throughput than existing methods. IONpath is showcasing the platform at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in Maryland from November 6-10.

See <https://www.ionpath.com/news/>

226. By announcing its formal commercial launch of its infringing MIBIScope after its knowledge of infringement, IONpath intended to, and did, sell the MIBIScope to third-parties, even though IONpath knew that the MIBIScope infringes on claims of the '698 Patent including, but not limited to, exemplary claim 6.

227. IONpath also hosted a booth, and through its founder Dr. Angelo presented, at the 2019 SITC Meeting recommending and teaching attendees of the conference on using the MIBIScope for its designed, and sole, purpose, which infringes on the '698 Patent including, but not limited to, exemplary claim 6. IONpath's co-presenters also detailed how IONpath representatives offered technical support to assist to the co-presenters institutions in using the MIBIScope to infringe on the '698 Patent including, but not limited to, exemplary claim 6.

228. IONpath also intentionally had its founders publish the 2020 Article and 2020 Review advertising, encouraging, and instructing third-parties on how to use the MIBIScope as a system infringing on the '698 Patent including, but not limited to, exemplary claim 6. In the 2020 Article, for example, IONpath detailed how the MIBIScope, as a system, infringed on at least exemplary claim 6 of the '698 Patent, by explaining to third-parties that the MIBIScope implements the "use of heavy metal-conjugated antibodies that are quantified by TOF MS, thus allowing highly multiplexed, single-cell and imaging assays." In the 2020 Review, for example, IONpath explained that its MIBI System was developed for the sole purpose of analyzing samples stained with antibodies tagged with metal-isotopes through a method wherein the sample has secondary ions released through the use of an ion beam raster scanned across the sample.

wherein the secondary ions are then passed through the detection system to complete the process,
which infringes on claims of the '698 Patent including, but not limited to, exemplary claim 6.

229. ~~168.~~ IONpath also offers for sale the MIBItag reagents which can be used to provide the sample including isotopically labelled antibodies for use with its infringing MIBIScope, and/or has encouraged the use of Fluidigm's proprietary Maxpar[®] Reagents with the MIBIScope. IONpath has published results obtained with the MIBIScope and identifying both the Maxpar[®] Reagents and MIBItags as the labeling reagents (in the 2018 Article referred to above, *see* Supplementary Material, page e1, Critical Commercial Assays).

STAR★METHODS

KEY RESOURCES TABLE

| | | |
|---|---------------------|----------------|
| Critical Commercial Assays | | |
| Maxpar X8 Antibody labeling kit | Fluidigm | Cat#2011XXX |
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| ImmPACT DAB (For HRP Substrate) | Vector Laboratories | Cat#SK-4105 |

230. ~~169.~~ In addition to directly infringing at least one claim of the '698 Patent including, but not limited to, exemplary claim 1,6, IONpath indirectly and intentionally infringes at least exemplary claim 16 of the '698 Patent by, among other things, instructing, directing, and/or requiring others, including customers, purchasers, users, and developers, ~~to use the system-claimed~~ through IONpath's commercial launch of the MIBIScope, presentations at the 2019 SITC Meeting, 2020 Article, and 2020 Review to use the MIBI System as set forth in at least exemplary claim 1,6, either literally and/or under the doctrine of equivalents, through ~~the sale of the MIBIScope, either alone or in combination with~~ the sale of the MIBIScope and MIBItags; where the claimed ~~systems are operated by either~~ system is used by IONpath or its customers,

purchasers, users, and developers, or some combination thereof. As of the October 11, 2019, when Fluidigm served IONpath with the First Amended Complaint, IONpath knew and/or was willfully blind to the fact that it was inducing others, including customers, purchasers, users, and developers, to infringe one or more claims of the '698 Patent by practicing, either themselves or in conjunction with IONpath, one or more system claims of the '698 Patent, through sales of the MIBIScope.

231. 170. After Fluidigm served IONpath with the First Amended Complaint on October 11, 2019, IONpath knowingly and actively aided and abetted the direct infringement of the '698 Patent by instructing and encouraging its customers, purchasers, users, and developers to use its MIBIScope product, including in combination with its MIBItag isotopically labelled antibodies. Such instructions and encouragement included, but are not limited to, advising third parties to use the MIBIScope in an infringing manner, including but not limited to use in combination with the MIBItag isotopically labelled antibodies, providing a mechanism through which third parties may infringe the '698 Patent, advertising and promoting the use of MIBIScope product alone and in combination with the MIBItags in an infringing manner, and distributing guidelines and instructions to third parties on how to use MIBIScope alone and in combination with the MIBItags in an infringing manner.

232. For example, IONpath's ~~2018 brochure "MIBIScope™ I: Multiplexed Tissue Imaging that Transforms Discovery"~~ advertises the benefits and advantages of the MIBIScope for performing mass cytometry methods, and describes how it may be used. IONpath's 2019 ~~"MIBI™ Reagents for High Multiplex Tissue Imaging (Get Results You Can Trust)"~~ advertises

~~the benefits and advantages of IONpath's isotopically conjugated antibodies (MIBItags), and described how they can be used for mass cytometry systems. IONpath's website also provides general instructions and explanations for the use of the MIBIScope, and the MIBItags, along with contact information for obtaining further information and/or ordering these products.~~ official commercial launch of the MIBIScope on November 5, 2019, after it was served with the Complaint in this action, promoted the purchase of the MIBIScope to image biomarkers within a sample through the use of staining a sample, removing a layer of the sample by directing an ion beam at a section of tissue with sufficient energy to generate secondary ions constituting "vaporizing, atomizing and ionizing" the metal labelled antibodies in a manner that infringes the claims of the '698 Patent. IONpath's CEO, Harris Fienberg, promoted, recommended, and encouraged using the MIBIScope to infringe on the '698 Patent to gain "unprecedented insights into spatial relationships with the tissue microenvironment by imaging and characterizing tissue samples at subcellular resolution." IONpath's CEO further admitted that prior to bringing the MIBIScope to market, IONpath piloted it with research and biopharma institutions instructing those institutions on how to use the MIBIScope by employing systems that infringe upon the '698 Patent.

233. By directing an ion beam at a section of tissue with sufficient energy to generate secondary ions, IONpath's MIBIScope is "vaporizing, atomizing and ionizing" the elemental tags of the lanthanide labeled antibodies in a manner that infringes the claims of the '698 Patent either literally and/or under the doctrine of equivalents. The 2019 Cell article to Keren describes and shows the creation of secondary ions from the elemental tags by directing the ion beam onto the

tissue sample. In so doing, the MIBIscope is directing ions at sufficiently high energies at the sample, such that the impact of the ions on the sample transfers energy to the sample, and this transfer of energy causes the elemental tags to become excited and liberated from the chemical moieties to which they are attached. The resulting excited and liberated elemental tags (i.e., the ionized lanthanide tags) are no longer in a solid or lattice matrix or in a solution and have been vaporized. The ionized metal tags have been liberated as constituent ionized atoms and have been atomized. The ionized metal tags have also been excited and thus have been vaporized, atomized, and ionized for purposes of the claims of the '698 Patent. Further, the MIBIscope is "vaporizing, atomizing, and ionizing" the elemental tags under the doctrine of equivalents because the ion beam liberates and excites the elemental tags so that the ionized elemental tags can be detected by mass spectrometry. As a result, the primary ion beam generates liberated secondary ions from the elemental tags for detection and performs substantially the same function in substantially the same way to obtain the same result. Accordingly, by promoting the purchase and use of the MIBIscope, and by providing instructing on how to use the instrument, IONpath has induced infringement of the '698 Patent.

234. ~~171.~~ As a direct and proximate result of IONpath's post-suit, indirect infringement of the '698 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm's lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

235. ~~172.~~ As a direct and proximate result of IONpath's post-suit acts of indirect infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath's infringing acts are enjoined and restrained by order of this Court.

COUNT X
CONTRIBUTORY PATENT INFRINGEMENT
(The '698 Patent)

236. ~~173.~~ Fluidigm incorporates by reference and realleges the averments set forth in the preceding paragraphs as if fully recited and incorporated herein.

237. ~~174.~~ IONpath has contributed and continues to contribute to the infringement of one or more claims of the '698 Patent under 35 U.S.C. § 271(c).

238. ~~175.~~ IONpath commercialized ~~its~~ a "purpose-built" MIBIScope ~~instrument~~ that is specially designed for, and only serves one purpose, which is implementing a method patented by Fluidigm "that uses secondary ion mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections" combined with "time-of-flight mass spectrometry," the operation of which results in the MIBIScope users infringing upon the system covered under one or more claims of the '698 Patent including, but not limited to, the system as set forth in, for example, exemplary claim ~~16~~ of the '698 Patent.

239. ~~176. On information and belief, beginning in 2018 or earlier, with an expected commercial launch date in 2019,~~ After Fluidigm served its First Amended Complaint alleging IONpath's infringement of the '698 Patent, IONpath knowingly, intentionally, and willfully ~~began marketing~~ continued to market and ~~selling~~ sell the infringing MIBIScope machine.

including, for example, the commercial launch on November 5, 2019, as well as presenting on, and selling, the MIBIScope at the 2019 SITC Meeting. The MIBIScope is a physical apparatus ~~containing the elements of Fluidigm's patented system~~ with a price tag at, or in excess of, \$1,000,000.00 specially designed to solely implement Fluidigm's methods set forth in the Patents.

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[See https://www.ionpath.com/news/](https://www.ionpath.com/news/)

240. The only purpose served by the MIBIScope is that of using “mass spectrometry to image antibodies tagged with isotopically pure elemental metal reporters in intact tissue sections” combined with “time-of-flight mass spectrometry.” The “antibodies tagged with isotopically pure elemental metal reporters” are the MIBItags (or Fluidigm’s Maxpar reagents), which are specifically created for that purpose. The antibodies are selected and engineered for their specific affinity for particular biomarkers of interest within a sample or cell. The selected antibodies are covalently linked to a particular type of polymer containing multiple binding sites for selected lanthanide tags, which allows them to serve their sole purpose and the sole purpose of the MIBIScope, which infringes at least exemplary claim 6 of the ‘698 Patent.

241. ~~177. On information and belief~~Accordingly, the MIBIscope is a “purpose-built” machine that does not serve any non-infringing use, but ~~instead corresponds to the system~~is solely designed to practice the method of at least ~~Claim 1~~exemplary claim 6 of the ‘698 patent.

242. ~~178.~~ IONpath has commercialized MIBItags which are isotopically labelled antibodies that can be used to provide the sample for analysis with the system of at least ~~Claim 1~~exemplary claim 6 of the ‘698 patent. When analyzing tissue cells with the MIBIscope, including but not limited to in combination with the MIBItags, the user infringes upon a patented system as set forth in, for example, exemplary claim 16 of the ‘698 Patent.

~~179.— On information and belief, beginning at least in 2019, IONpath began marketing and selling the infringing MIBItags. The MIBItags are isotopically labelled antibodies designed for implementation with Fluidigm’s patented system.—~~

243. ~~180. On information and belief, the~~The MIBItags are specifically designed for use in the infringing methods of the ‘698 Patent and do not serve any non-infringing use.

244. ~~181.~~ As a direct and proximate result of IONpath’s post-suit contributory infringement of the ‘698 Patent, Fluidigm has suffered and continues to suffer damage. Fluidigm is entitled to recover from IONpath Fluidigm’s lost profits, and no less than a reasonable royalty, in an amount to be determined at trial.

245. ~~182.~~ As a direct and proximate result of IONpath’s post-suit acts of contributory infringement, Fluidigm has been irreparably harmed and will continue to be harmed unless and until IONpath’s infringing acts are enjoined and restrained by order of this Court.

PRAYER FOR RELIEF

Wherefore, Fluidigm respectfully requests that this Court enter judgment and provide relief as follows:

A. Enter a judgment that IONpath has directly infringed and is directly infringing one or more claims of the ‘386 Patent, the ‘104 Patent, and the ‘698 Patent;

B. Enter a judgment that, post-suit, IONpath has indirectly infringed and is indirectly infringing by inducing others to infringe on one or more claims of the ‘386 Patent, the ‘104 Patent, and the ‘698 Patent;

C. Enter a judgment that, post-suit, IONpath has contributed and is contributing to the infringement of one or more claims of the ‘386 Patent, the ‘104 Patent, and the ‘698 Patent;

D. That Fluidigm be awarded damages against IONpath pursuant to 35 U.S.C. § 284 that are adequate to compensate Fluidigm for IONpath’s infringement, or inducement thereof, of Fluidigm’s ‘386 Patent, ‘104 Patent, and ‘698 Patent, but in no event less than a reasonable royalty for the use made of the claimed inventions together with interest and costs;

E. Permanently enjoin, under 35 U.S.C. § 283, IONpath, its officers, agents, servants, employees, attorneys, successors, and assigns and all other persons in active concert or participation with any of them from infringing the ‘386 Patent, ‘104 Patent, and ‘698 Patent;

F. Permanently enjoin, under 35 U.S.C. § 283, IONpath, its officers, agents, servants, employees, attorneys, successors, and assigns and all other persons in active concert or participation with any of them from inducing third parties into infringing the ‘386 Patent, ‘104 Patent, and ‘698 Patent;

G. Declare that IONpath's infringement was and is willful from the time it became aware of the infringing nature of its product and awarding treble damages for the period of such willful infringement of the '386 Patent, '104 Patent, and '698 Patent, pursuant to 35 U.S.C. § 284;

H. Declare this an exceptional case within the meaning of 35 U.S.C. § 285 and award Fluidigm their reasonable attorneys' fees, costs, and expenses;

I. An accounting of all infringing sales and revenues, together with post judgment interest and prejudgment interest from the first date of infringement, of the '386 Patent, '104 Patent, and '698 Patent;

J. Award Fluidigm compensation, monetary damages and punitive damages for IONpath's intentional interference with Fluidigm's contractual relations, in an amount to be ascertained at trial, together with interest thereon;

K. Award Fluidigm pre-judgment and post-judgment interest on the damages awarded;

L. Award Fluidigm its costs and reasonable attorneys' fees, expenses and costs, incurred in connection with this action; and

M. Award Fluidigm any and all further legal and equitable relief that the Court may deem just and proper under the circumstances.

DEMAND FOR JURY TRIAL

Fluidigm hereby respectfully requests a trial by jury on all issues raised in this Complaint so triable by right pursuant to Rule 38(b) of the Federal Rules of Civil Procedure.

Dated: ~~October 11, 2019~~ February 13, 2020 K. Lee Marshall
BRYAN CAVE LEIGHTON PAISNER LLP

By: /s/ K. Lee Marshall
K. Lee Marshall

*Attorneys for Fluidigm Corporation
and Fluidigm Canada Inc.*